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Freezing of Gait in Parkinson's Disease

by

Marguerite Wieler

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of *Master of Science*

in

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ABSTRACT

Parkinson's disease (PD) is a slowly progressive neurologic disorder characterized by tremor, slowness, stiffness, poor balance and difficulty walking. Medications, particularly levodopa, improve many symptoms of PD. However, gait difficulties do not respond well to any intervention. Freezing of gait (FOG) responds very poorly to all interventions. FOG describes the transient inability to take a step on a background of relatively normal movement. People describe their feet feeling "glued" to the ground. Preliminary data in the literature suggested injections of botulinum toxin A (BTX-A) into calf muscles decreased FOG frequency and severity in parkinsonism. This study examined effects of BTX-A injections versus placebo (saline) in a double blind crossover fashion in 12 subjects with Parkinson's disease and debilitating FOG. A variety of clinical assessments looking at FOG, detected no significant differences between BTX-A and placebo injections. Our results fail to demonstrate an objective improvement in FOG associated with BTX-A injection.

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there was a very bad disease!); the technical and artistic assistance from my sister, Anna, who often responded to desperate cries for immediate help; the database connection and support of my efforts in science from my brother, David; the listening ear and general advise from my big brother, Fred, whose offer to videotape my convocation ceremony ensured completion of this project; and for the interest, support and assistance in celebrating from Susan and Charlene. And finally, thanks to Felix, Forrest, Madeleine, Hannah and Benson for making me smile.

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List of Abbreviations

FOG	freezing of gait
GPi	globus pallidus internus
GPe	globus pallidus externus
STN	subthalamic nucleus
SNpr	substantia nigra pars reticulata
SNpc	substantia nigra pars compacta
GABA	gamma-aminobutyric acid
MC	motor cortex
SMA	supplemental motor area
PMC	premotor cortex;
VL	ventrolateral.
COMT	catechol-O-methyl transferase
ADL	activities of daily living
MAO-B	monoamine oxidase type B
DATATOP	Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism
DBS	deep-brain stimulation
EMG	electromyography
UPDRS	Unified Parkinson's Disease Rating Scale
FOGQ	Freezing of Gait Questionnaire
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MIS	modified inverted walking stick
BTX	Botulinum toxin
SNAP-25	synaptosome-associated protein-25
SNARE	soluble N-ethyl-maleimide-sensitive factor attachment protein receptor
Ach	acetylcholine
BTX-A	Botulinum toxin Type A
LD_{50}	Lethal Dose 50
MDC	Movement Disorders Clinic
M	male
F	female
L	levodopa
CR	levodopa controlled release
P	pergolide
Px	pramipexole
R	ropinirole
E	entacapone
A	amantadine
S	selegiline
T	trihexyphenidyl
B	bromocriptine

1 Introduction

Parkinson's disease is a slowly progressive neurologic disorder caused by degeneration of dopaminergic neurons in the substantia nigra. Tremor, bradykinesia, rigidity, postural instability and gait disturbance are cardinal features of Parkinson's disease. Pharmaceutical interventions, particularly levodopa, are used to ameliorate many of the symptoms of Parkinson's disease. As the disease progresses, difficulty in performing motor tasks required for activities of daily living increases and results in significant disability. With more advanced disease, medications become essential for controlling the parkinsonian symptoms (Giladi et al., 1992b; Lamberti et al., 1997; Nieuwboer et al., 1998). Gait difficulties, often a significantly disabling feature of Parkinson's disease, are particularly resistant to treatment. Freezing, seen in more advanced disease and disease of longer duration, is considered to be a major feature of parkinsonism (Giladi and Fahn, 1998), though the mechanisms underlying freezing remain unknown. Primarily seen during gait, freezing has also been reported during speech, handwriting and when brushing teeth. Freezing of gait (FOG) in Parkinson's disease is a disabling feature that responds unsatisfactorily to medical intervention (pharmaceutical or surgical) and inconsistently to sensory, behavioural and cognitive "tricks" (Fahn, 1995b). Preliminary data in the literature suggested that botulinum toxin injections into calf muscles had a positive effect on the severity and/or frequency of freezing of gait episodes in parkinsonism. This intriguing and novel approach to treating FOG warranted further investigation. This study examined the effects of botulinum toxin injections on FOG in Parkinson's disease in a double-blind, placebo-controlled crossover study.

2 Parkinson's disease

James Parkinson, in 1817, first described the constellation of symptoms that now bear his name in "An Essay on the Shaking Palsy". Parkinson's disease is a chronic, progressive, neurodegenerative movement disorder defined by the presence of tremor, rigidity and bradykinesia. Despite the progressive nature of this disease, most people living with Parkinson's disease maintain healthy lives for many years. Current treatment and management approaches prevent many of the difficulties that in the past contributed to significant immobility-related disability. A combination of medical management, exercise, proper nutrition and adequate support can help to maintain and/or improve function.

2.1 Epidemiology

Parkinson's disease is a relatively common disorder with an estimated prevalence of 244/100,000 in Alberta. (Svenson et al., 1993) There appears to be geographical variation in the prevalence rate with Parkinson's disease found more commonly in North America and Europe than in Japan, China and Africa, suggesting a greater risk for Parkinson's disease in Caucasians. Alternatively, differences in prevalence may be explained by study methodology including how the population was surveyed (door-to-door, health care records, national health registries etc.), age-groups studied and diagnostic criteria (Tanner et al., 1997). If there are geographical differences in the appearance of Parkinson's disease, this may suggest shared environmental exposure as a risk factor. The underdiagnosis or misdiagnosis of Parkinson's disease will affect studies of incidence and prevalence. Although the diagnosis of Parkinson's disease is made on the basis of clinical criteria, the gold standard for diagnosis is on autopsy examination. The diagnosis of Parkinson's disease was found to be incorrect in approximately 24 percent of cases at autopsy (Rajput et al., 1991) but a more recent study suggested a rate of as low as 10 percent (Hughes et al., 2001). Various factors have been identified as being associated with an

increased risk for Parkinson's disease. These are summarized in Table 1 and expanded upon below.

Table 1 Factors Associated with Increased Risk for Parkinson's disease (Tanner et al., 1997)

Aging, gender (men), and race (Caucasian)
Family history of Parkinson's disease
Life experience
▪ Trauma
▪ Emotional stress
▪ Personality (shyness and depressiveness)
Environmental exposures
▪ Metals (manganese, iron)
▪ Drinking well water
▪ Farming
▪ Rural residence
▪ Wood pulp mills
▪ Steel alloy industries
▪ Herbicide and pesticide exposure (dieldrin)
▪ MPTP and MPTP-like compounds
Infectious agents

Gender does not seem to be a significant risk factor for the development of Parkinson's disease with most studies showing men and women being affected in approximately equal numbers. However, there are some studies that show a slight preponderance in males (Tanner et al., 1997).

While Parkinson's disease is most commonly diagnosed after the age of 50, up to 10% have onset of symptoms before the age of 40 (Hoehn, 1967). The incidence and prevalence of this disease increases with age, and may be explained, in part, by the normal age-related decline in nigral cells and endogenous dopamine stores (Tanner, 1992).

Exposure to environmental toxins has been associated with the development of Parkinson's disease. The identified risk factors include rural living, farming, drinking well water and exposure to herbicides and pesticides (Jenner, 2001).

The significance of these results must be interpreted with caution as the studies were sufficiently different to prevent direct comparisons and an association cannot necessarily be considered as causal (Tanner, 1992).

A number of other suggested risk factors for Parkinson's disease include infection (Tsui, 1999), trauma (head trauma with or without loss of consciousness) (Bower et al., 2003), premorbid personality and emotional stress. There have been no strong studies that convincingly support these as factors altering the risk of Parkinson's disease (Tanner, 1992).

Potentially protective factors have also been identified in many case-controlled studies, including foods high in tocopheral (Vitamin E), cigarette smoking and caffeine (Hernán et al., 2002). The significance of this association remains unknown (Tanner et al., 1997).

The role of genetics and heredity in Parkinson's disease remains unclear. There are documented cases of familial Parkinson's disease (Golbe et al., 1990) but there is conflicting evidence from identical twin studies. Duvoisin (1986) failed to show that development of Parkinson's disease in one twin influenced its development in the other, while Tanner et al. (1999) suggested a strong role of inheritance of Parkinson's disease in twins before the age of 50 but weaker evidence for its role when onset was beyond that age. To date, eleven Parkinson's disease genes and loci have been identified (Dekker et al., 2003) but genetic factors appear to be only one of many involved in the development of Parkinson's disease.

Based on the knowledge accumulated to date, it would appear that a combination of environmental exposure to a variety of risk factors in conjunction with genetic influence would best explain the development of Parkinson's disease but, at present, its etiology is incompletely understood.

2.2 Pathogenesis

Parkinson's disease is a hypokinetic disorder where bradykinesia (lack of spontaneous movements) and rigidity are primary features resulting from dysfunction in the nigrostriatal dopaminergic pathways in the basal ganglia.

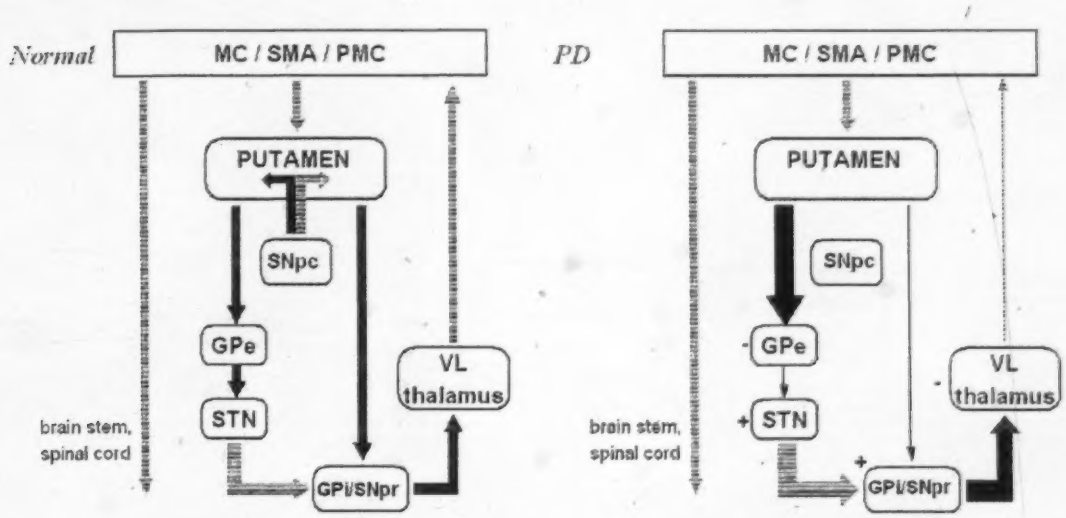
2.2.1 Basal Ganglia

Comprised of a number of subcortical nuclei (the putamen, caudate, globus pallidus internus (GPi) and externus (GPe), subthalamic nucleus (STN), and substantia nigra pars reticulata (SNpr) and pars compacta (SNpc)), the basal ganglia have connections to many parts of the brain. The basal ganglia are important in the organization and regulation of motor behaviour. They play a crucial role in the initiation and control of movement and posture. In spite of the absence of a direct connection to the alpha or gamma motor systems, input from the motor cortex, other areas of the cortex, and thalamus are processed by the basal ganglia and indirectly influence motor output systems. Despite considerable research, the complex circuitry of the basal ganglia remains poorly understood and models continue to evolve (Albin et al., 1989; Lang and Lozano, 1998). The limitations of the current models are evidenced by their lack of consideration of other brain structures such as the pedunculopontine nuclei, which may be particularly important for gait and freezing. Numerous neurotransmitters, including dopamine, glutamate, acetylcholine, enkephalin, and gamma-aminobutyric acid (GABA), exert inhibitory or excitatory influences on multiple pathways involving the basal ganglia. The balanced action of these neurotransmitters ensures normal functioning of the basal ganglia with a net inhibitory effect on the thalamus.

The main afferent nuclei are the caudate and the putamen (striatum) with widespread connections from the motor, sensory and association areas of the cortex, thalamus, locus ceruleus and raphe nuclei. The major efferent projections are from GPi and SNpr to the thalamus and brain stem, including the pedunculopontine nuclei. There are extensive interconnections with both inhibitory and excitatory pathways within the basal ganglia.

Recent models have been proposed to explain both normal motor control and the abnormal motor control seen in Parkinson's disease. (See Figure 1.) The loss of dopaminergic neurons in the SNpc results in overactivity of the GPi and STN. The GPi primarily exerts an inhibitory effect with major projections to the thalamus and brainstem. Two separate circuits within the striatum - a direct and an indirect pathway, act upon the GPi.

Figure 1 Schematic of changes in basal ganglia circuitry in Parkinson's disease (adapted from Albin et al., 1989)



The solid line indicates an inhibitory pathway. A hatched line indicates an excitatory pathway. (MC - motor cortex; SMA - supplemental motor area; PMC - premotor cortex; VL - ventrolateral.) In normal striatal circuitry, the output from the GPi exerts a chronic inhibitory effect on the thalamocortical neurons (VL thalamus). Activation of the direct pathway inhibits firing of the GPi, whereas activation of the indirect pathway (through the GPe and STN) stimulates it. Dopamine from the SNpc acts on the direct and indirect pathways. In Parkinson's disease (PD), decreased striatal dopaminergic input, secondary to degeneration of SNpc neurons, reduces the inhibition of the GPi by the direct pathway and increases excitation of the GPi via the indirect pathway. The net result is an excessive inhibition of VL thalamus and subsequent diminished output to the cortical motor regions.

The direct pathway from the putamen to the GPi is inhibitory. The GPi exerts an inhibitory influence on the thalamus, which in turn project to the cortex and brainstem (Alexander et al., 1990). Excitatory input from the SNpc and cortex results in net inhibition of the GPi. The resulting disinhibition of the thalamus increases excitation of the precentral motor regions in the cortex that may facilitate cortically initiated movement (Albin et al., 1989).

The putamen also provides inhibitory input to the GPe. The GPe in turn sends inhibitory projections to the STN, which sends excitatory projections to the GPi. Stimulation of this indirect pathway exerts a net inhibitory effect on the excitatory output of the STN on the GPi. This results in an overall decrease in the inhibitory influence of the GPi on the thalamus and facilitates initiation of movement. Decreased dopamine in the basal ganglia in Parkinson's disease results in under-activity of the direct pathways and over-activity of the indirect pathways with a net increase in the inhibition of thalamic output and subsequent reduction of activity in the cortex (Albin et al., 1989).

This model of basal ganglia function is derived primarily from observation of disease states and animal models known to disrupt the basal ganglia. How this disruption of the normal functioning of the basal ganglia impacts cortical output remains speculative. The supplemental motor area (SMA) of the cortex appears to be involved in the preparation of sub-movements of a motor sequence or plan. The SMA connections to the basal ganglia influence the correct timing of the sub-movements that are part of a whole movement sequence. The premotor area (PMA) of the cortex and the SMA also play a role in preparing for whole motor sequences that are skilled or learned in nature (Iansek et al., 1995). The SMA and PMA are involved with the basal ganglia in the initiation and running of motor programs. When the basal ganglia are functioning abnormally in Parkinson's disease, the initiation and execution of motor sequences are disrupted, resulting in movements that are reduced in amplitude and are slower. The incremental breakdown of the sub-movements of a motor program result in progressive slowing or speeding of movements (as seen in the gait disturbance of festination). The movement plans may be miniaturized (as manifest in micrographia - miniaturization of handwriting - and decreased stride length) and the ability to switch between plans is impaired. The reduction of movement speed and amplitude is manifested in voluntary movements, particularly those involving internally-generated, skilled motor programs like walking, posture,

speech and manual dexterity and manipulation (Iansek et al., 1995). People with Parkinson's disease are unable to modify movement patterns in response to changing demands of a task.

It is important to recognize there are also other projections to and from the nuclei (multiple parallel, segregated circuits that modify and modulate information) that are involved with cognitive, behavioural (Alexander et al., 1986) and emotional function via the limbic system (Alheid and Heimer, 1988). A detailed discussion of these is beyond the scope of this paper but the susceptibility of transient improvement or worsening of the symptoms of Parkinson's disease to general arousal and stress, as well as impairment of the ability to perform dual tasks (O'Shea et al., 2002; Marchese et al., 2003) implicate these connections of the basal ganglia in the performance of motor programs.

Despite advances in the current understanding of the circuitry of the basal ganglia, the impact of the degeneration of dopamine producing neurons and the availability of various treatment and management strategies, the underlying cause of Parkinson's disease remains a mystery and a cure has yet to be discovered.

2.3 Diagnosing Parkinson's disease

Although the *pathological* definition of Parkinson's disease includes significant loss of pigmented, dopamine-producing cells in the substantia nigra and the presence of Lewy bodies (intracytoplasmic protein aggregates) (Jenner, 2001), the *clinical* diagnosis is made on the basis of history and clinical examination. To date, laboratory tests and imaging techniques are helpful in excluding other processes that may present with parkinsonian symptoms but none can definitively diagnose Parkinson's disease. Not everyone presenting with parkinsonian symptoms will have Parkinson's disease. The constellation of motor impairments, that includes bradykinesia, rigidity and postural instability, can be caused by any number of conditions that disrupt the nigrostriatal circuitry

in the basal ganglia secondary to a decrease in available dopamine. These other causes include structural lesions, metabolic disorders, exposure to toxins, drugs that interfere with the dopamine pathways in the basal ganglia, parkinson-plus syndromes and hereditary disorders. Each will have a different prognosis and treatment path from Parkinson's disease. (See Table 2.) Distinguishing idiopathic Parkinson's disease from other causes without the benefit of autopsy confirmation makes it an inexact science with 10% or more of cases being misdiagnosed (Rajput et al., 1991; Hughes et al., 2001).

Table 2 Classification of Parkinsonism (adapted from Paulson and Stern, 1997)

Primary (idiopathic)
▪ Parkinson's disease
Secondary (symptomatic)
▪ Drug-induced
▪ Infectious
▪ Structural
▪ Toxin
▪ Vascular
Parkinsonism-plus syndromes
▪ Cortical-basal ganglionic degeneration
▪ Hemiparkinsonism-hemiatrophy
▪ Dementia syndromes, like Alzheimer's disease and Dementia with Lewy Bodies
▪ Multiple-system atrophy
▪ Parkinsonism-dementia-ALS complex of Guam
▪ Progressive supranuclear palsy
Hereditary degenerative diseases
▪ Autosomal-dominant cerebellar ataxias
▪ Hallervorden-Spatz disease
▪ Huntington's disease
▪ Mitochondriopathies
▪ Neuroanthocytosis
▪ Wilson's disease

2.3.1 Idiopathic Parkinson's disease

The clinical diagnosis of idiopathic Parkinson's disease is based on the presence of parkinsonian symptoms and the absence of other explanatory causes. The

cardinal signs of parkinsonism include tremor at rest, rigidity, bradykinesia, and loss of postural reflexes. It has been suggested that freezing of gait be included as the fifth cardinal sign as this phenomenon is associated with many parkinsonian syndromes (Giladi and Fahn, 1998). There are many parkinsonian syndromes that can present in a similar fashion as noted previously. It is important, however, to try to make an accurate diagnosis as this may influence treatment decisions. A useful guideline for making a diagnosis is the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria (Gelb et al., 1999). The criteria include establishing the presence of a parkinsonian syndrome, outline exclusionary criteria and finally require that three or more inclusion criteria be met. The inclusion criteria include unilateral onset, rest tremor, progression of symptoms, persistent asymmetry with the side of onset remaining most affected, excellent response to levodopa, response to levodopa for at least 5 years, severe levodopa-induced dyskinesia and a clinical course of 10 years or longer. Recent data suggest that high specificity of approaching 93% can be achieved in diagnosis (Hughes et al., 2001). Manifestations of Parkinson's disease usually begin unilaterally and marked asymmetry of motor involvement may continue as the disease progresses. The cardinal parkinsonian symptoms are described in the following section.

2.3.2 Cardinal Symptoms of Parkinson's disease

2.3.2.1 Tremor

The feature most identified by the public with Parkinson's disease is tremor and was, indeed, the topic of the essay by James Parkinson "An essay on the Shaking Palsy". In approximately 70% of cases, the appearance of a unilateral rest tremor is the presenting sign of Parkinson's disease (Hoehn and Yahr, 1967). The tremor in the hand is often described as "pin-rolling" involving the thumb and index finger. Tremor usually starts in one limb but as the disease progresses may spread to involve all limbs as well as the chin. It is called a rest tremor because it often it attenuated with motor activity in the affected segment.

Abating during sleep, tremor is commonly exacerbated by stress and is often cited as a socially disabling feature of Parkinson's disease.

2.3.2.2 Rigidity

Rigidity describes an increase in resting muscle tone observed as resistance throughout the range of passive movement. Although present on examination, it does not appear to play a major role in disability or impairment. Indeed, many people are unaware of any increase in stiffness (Iansek et al., 1997).

2.3.2.3 Bradykinesia

Bradykinesia and akinesia are characterized by a decreased ability to initiate and perform purposeful, voluntary movements. Specifically, bradykinesia refers to slowness of ongoing movements and akinesia to the complete failure of willed movement to occur (Hallett, 2003). Any phase of movement can be affected including initiation, alteration in direction and the ability to stop a movement once it has begun. Also typically seen as a result of bradykinesia/akinesia is diminution of spontaneous movements (facial expression, small postural adjustments in response to perturbations) and associated movements (arm swing while walking). The impairment in initiating and completing motor programs is seen during gait as an ignition problem and during freezing episodes. Both of these can lead to significant disability.

2.3.2.4 Postural Instability

Postural control allows individuals to maintain their balance (equilibrium) and an upright posture by appropriately processing information from the somatosensory, visual and vestibular systems. In Parkinson's disease, the ability to process this information is disturbed and an inability to respond appropriately to an external perturbation is often seen (Bronte-Stewart et al., 2002). Automatic postural adjustments are reduced or absent and this disruption of anticipatory postural activity is a leading cause of falls in this population and a disabling feature of the disease.

2.3.2.5 Gait Disorder

Although not usually a presenting symptom of Parkinson's disease, as time goes on, a distinct gait pattern emerges. Asymmetric, reduced arm swing may be the first abnormality that is seen with gait. Typically, gait is characterized by a stooped posture, short, shuffling steps with a narrowed base of support, slow turns and a tendency to festinate. In more advanced disease, freezing episodes emerge and present a difficult management problem (Giladi et al., 2001b). The gait disturbances seen in Parkinson's disease are discussed in greater detail in Chapter 4.

2.3.3 Secondary Symptoms

While primarily identified as a movement disorder, there are several other symptoms that occur in this population (See Table 3.) These so-called secondary symptoms involve not only motor disruption but also non-motor disturbances of the autonomic and sensory systems, mood and anxiety and may cause significant difficulties in daily functioning.

2.4 Management of Parkinson's disease

The goal of management in Parkinson's disease is to achieve the best quality of life possible by ameliorating motor impairments and introducing compensatory strategies when symptoms can no longer be optimally controlled.

The mainstay of symptomatic treatment uses pharmacological interventions with the goal of improving motor difficulties caused by decreased levels of dopamine in the brain. Initially, most patients respond well to these interventions with nearly normal motor performance maintained for a significant time. The medications most often implemented in the treatment of Parkinson's disease are discussed next.

Table 3 Secondary Manifestations of Parkinson's disease (adapted from Paulson and Stern, 1997)

Cognitive/Behavioural manifestations
▪ Anxiety
▪ Dementia
▪ Depression
▪ Sleep disturbance
Musculoskeletal
▪ Kyphoscoliosis
▪ Peripheral edema
▪ Compression neuropathies
▪ Hand and foot deformities
Autonomic
▪ Constipation
▪ Orthostatic hypotension (light-headedness)
▪ Increased sweating
▪ Sexual/urinary dysfunction
▪ Urinary dysfunction
Sensory
▪ Cramps
▪ Pain
▪ Paresthesias
Cranial nerve/facial
▪ Dysarthria
▪ Dysphagia
▪ Sialorrhea
Skin
▪ Seborrhea

2.4.1 Medical Management

2.4.1.1 Pharmaceutical

2.4.1.1.1 Levodopa

The single most effective treatment for the symptoms of Parkinson's disease remains levodopa. First introduced as an antiparkinsonian therapy in the 1960's, virtually every patient with Parkinson's disease derives significant benefit from it, at least initially. Unfortunately, significant and often disabling motor complications (discussed below) are often associated with long-term exposure to

levodopa. Levodopa crosses the blood-brain barrier into the central nervous system where it is decarboxylated to form dopamine. Peripheral metabolism of levodopa can lead to severe side effects (including nausea and vomiting), which can be decreased by blocking peripheral metabolism with the decarboxylase inhibitors carbidopa or benserazide. The enzyme catechol-O-methyl transferase (COMT) is responsible for the methylation of levodopa, reducing its central nervous system bioavailability by up to 90% (Kurth and Adler, 1998). COMT inhibitors, such as entacapone, increase levodopa available to the brain but can increase central dopaminergic side effects.

2.4.1.1.2 Dopamine agonists

While the combination of levodopa, decarboxylase inhibitors and COMT inhibitors provide and enhance exogenous delivery of dopamine to the brain, dopamine agonists directly stimulate the dopamine receptors in the basal ganglia. Bromocriptine, pergolide, ropinirole and pramipexole are available as mono- or adjunct- therapy to alleviate parkinsonian symptoms. Dopamine agonists have been associated with a decrease in the development of motor complications when used as monotherapy in early disease (Rascol, et al. 2000; Parkinson Study Group, 2000). They are also useful in conjunction with levodopa in later stages. A recently published practice parameter (Miyasaki et al., 2000) concluded the following: 1) levodopa, ropinirole, and pramipexole are effective in ameliorating motor and activities of daily living (ADL) disability in patients with Parkinson's disease who require dopaminergic therapy; 2) levodopa is more effective than ropinirole and pramipexole in treating the motor and ADL features of Parkinson's disease; and 3) ropinirole and pramipexole treatment result in fewer motor complications than levodopa after 2.5 years of follow-up.

2.4.1.1.3 Other Treatments

Medications aimed at increasing the action of dopamine are the mainstay of treatment in Parkinson's disease but they do not provide uniform and sustained improvement for all parkinsonian symptoms. Gait disturbances are particularly resistant to treatment. A number of other drugs are available as adjunct therapy.

Anticholinergic medications (trihexypenidyl, benztropine, and procyclidine) may play a role in treating parkinsonian features by decreasing the activity of acetylcholine and restoring the dopamine-acetylcholine balance. Selegiline may prolong the central effects of levodopa by inhibiting central metabolism by monoamine oxidase type B (MAO-B). It has been proposed that selegiline might have a neuroprotective action. In the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) study (Parkinson's Study Group, 1989), selegiline was found to reduce the risk of developing disability requiring levodopa therapy by 50 percent. Unfortunately, this was not sustained during the washout period suggesting a symptomatic benefit rather than a neuroprotective one. The antiviral agent amantadine is used to treat parkinsonian symptoms as monotherapy or in combination with other antiparkinsonian drugs. It is thought to work either by blocking the reuptake of dopamine, by increasing the release of endogenous, or through excitatory amino acid channel antagonism. Its mechanism of action is not well understood but it also appears to have an ameliorating effect on levodopa-induced dyskinesia (Metman et al., 1999). None of these medications are as effective as levodopa itself but may be of use in mildly symptomatic patients or as adjunct therapy in advanced patients where the side effects must be weighed against potential benefits.

Unfortunately, as Parkinson's disease progresses, medications become less able to control the motor impairments and become less predictable and/or effective in their action. Parkinsonian features may become more severe; postural instability and gait disturbances may become more problematic. Many of these complications are distressing to the patient because they present significant functional disability and are unpredictable in nature.

A common problem of later disease is that of motor fluctuations. This refers to alternating periods of good response to medication with reasonably good mobility ("on" periods), with periods of significant motor impairment ("off" periods). These

motor fluctuations may be rapid and seemingly unrelated to the timing of antiparkinsonian medication.

The most common type of motor fluctuation occurs because the antiparkinsonian response to levodopa becomes shorter as the disease progresses. Patients experience its effect "wearing-off" before the next dose of medication is due. This end-of-dose deterioration can result in significant disability.

A seemingly paradoxical side-effect of long-term exposure to levodopa is the emergence of abnormal involuntary movements called dyskinesias. Typically choreiform (rapid and/or jerky) in nature, dystonic (sustained muscle contractions) feature may also be present. Dyskinesia may occur in both "on" and "off" periods. They can be relatively mild in presentation or severely disabling. Dyskinesias present a significant management issue.

The challenge of managing the symptoms of later stage Parkinson's disease with pharmacological interventions may lead to considerations of surgical options.

2.4.1.2 Surgical Management

Prior to the advent of levodopa therapy for Parkinson's disease, surgical interventions were employed to alleviate symptoms. These procedures fell out of favour when levodopa was introduced into the treatment armamentarium. As it became clear that levodopa was not the complete cure some had thought it would be and, with the emergence of a better understanding of the basal ganglia physiology (Alexander et al., 1986) and precise and sophisticated imaging techniques, surgical interventions have enjoyed resurgence in the treatment of Parkinson's disease.

Pallidotomy and thalamotomy involve thermal lesioning of specific targets in the GPi and thalamus. Thalamotomy is effective in controlling tremor while pallidotomy has been shown to be effective in improving bradykinesia and rigidity

in the "off" state and dyskinesia. No improvements in parkinsonian features are seen beyond those seen with the best response to levodopa (Alkhani and Lozano, 2001). Neither procedure has a significant impact on axial symptoms and gait problems are not improved. The magnitude of symptom relief appears to be associated with both lesion location and size (Van Horn et al., 2001) with the beneficial effects lasting years (Vitek et al., 2003). These procedures are usually unilateral due to the complications associated with symmetrical lesions in the brain and, thus, the benefit is primarily seen on the side contralateral to the lesion. While many patients have improved motor function following these procedures (particularly in the "off" state), the bilateral nature of Parkinson's disease renders this approach sub-optimal and gait disturbances remain unchanged following these procedures.

In recent years, high-frequency stimulation of various brain targets (GPi, STN and thalamus) has provided more comprehensive improvement of symptoms in selected patients with advanced Parkinson's disease. Deep-brain stimulation (DBS) allows for bilateral stimulation of the brain and may result in more positive outcomes than the unilateral procedures. DBS involves the insertion of leads into the appropriate target that are, in turn, connected, subcutaneously, to an implanted pulse generator. In contrast to the permanent, fixed lesion of pallidotomy and thalamotomy, an external DBS programmer allows the clinician to effectively "shape" the area of stimulation to provide optimal symptom control. The ideal target has yet to be confirmed but studies of DBS in GPi and STN show that both are effective in treating the cardinal signs of Parkinson's disease as well as motor fluctuations and dyskinesia (Pahwa and Lyons, 2003). There are contradictory data and no consensus on the effectiveness of DBS for axial symptoms and gait disorders (Stolze et al., 2001; Ferrarin et al., 2002; Defebvre et al., 2002).

An intriguing possibility for treating the spectrum of symptoms seen in Parkinson's disease is to replace the defunct dopamine-producing neurons thus

eliminating the need for pharmacological or DBS intervention. A number of studies have looked at the efficacy of transplanting fetal mesencephalic grafts into the striatum (Freed et al., 1992, 2001; Olanow CW, 1997, 2001). The results for symptom control have been mixed and the transplanted cells do not appear to function as normal nigral cells.

Another emerging area of research uses embryonic or neural stem cells as a method of producing dopamine neurons for transplantation. There are also many challenges with this approach, including the need to control cell proliferation and differentiation. These techniques, while promising, remain experimental.

2.4.2 Non-pharmacologic Treatment

The progressive, neurodegenerative nature of Parkinson's disease means that symptoms become increasingly more disabling over time. Pharmacological interventions, individually tailored, remain the mainstay of treatment. There are, however, issues facing the person with Parkinson's disease that are not addressed by medications. Rehabilitation services and psychosocial support are important components of the holistic management approach to Parkinson's disease. A multidisciplinary team approach is essential with members of the team varying according to the needs of the individual, and his or her family, changing as the disease progresses and different issues emerge. This team may include any combination of physicians, physical therapists, occupational therapists, speech-language pathologists, nurses, social workers, dieticians, psychologists and community support groups. Appropriate at various points in the disease, each of these services may provide coping and management strategies. The overall goal is to allow the individual to achieve the highest possible level of independent function with this level inevitably changing as physical and/or cognitive abilities decline and the effectiveness of medication changes.

While it makes intuitive sense that rehabilitation services are beneficial in the treatment of Parkinson's disease and there is, indeed, evidence that patients may benefit from physical and occupational therapy in conjunction with medications (de Goede et al., 2001; Goetz et al., 2002), studies of physical and occupational therapy in Parkinson's disease all suffer from small numbers, lack of consensus as to "best practice" and difficulty in designing large, randomized placebo-controlled trials that would establish evidence-based interventions (Deane et al., 2002a, 2002b).

The goal of physical therapy in Parkinson's disease is to address the symptoms that are modifiable, to minimize secondary complications, and to teach preventative strategies where indicated (Schenkman and Butler, 1989; Schenkman et al , 1989). Physical therapy stresses activities that enhance the performance of functional motor tasks, including walking, turning, going from sit to stand, bed mobility, fall prevention, posture, reaching, grasping and manipulating objects, as well as general conditioning, strength and flexibility (Morris, 2000; Scandalis et al., 2001). Various studies have shown that individuals with Parkinson's disease move with greater ease in the presence of external sensory cues (Morris, 1994; Behrman et al., 1998; Marchese et al., 2000) and this, coupled with the principles of task and context specific learning (Schmidt, 1999) helps to guide physical therapy intervention. (Some of these strategies that specifically relate to gait are explored more comprehensively in the Chapter 5.)

In conclusion, at all stages of the disease, it is crucial to emphasize the goal of treatment in Parkinson's disease, pharmacologic and non-pharmacologic, is not necessarily to achieve a "normal" state but rather to achieve and maintain the highest possible level of independent function. The components of this management will vary from individual to individual and with change in response to the changing needs of the person living with Parkinson's disease.

3 Gait

Most of us take walking for granted. Human gait involves a complex interaction of various sensory and motor systems requiring exquisite precision and coordination to allow movement in an upright posture. Successful gait requires the ability to assume an upright posture and support the body against gravity, the ability to generate, initiate and maintain a basic locomotor pattern that can progress the body in the desired direction and the ability to adapt the gait pattern to meet the demands of the environment and the individual's goals. Our understanding of the control mechanisms of human gait continues to evolve. Both central and peripheral inputs play roles in the control of locomotion. The essential peripheral inputs are from the sensory (proprioceptive, vestibular and visual) system and outputs from the motor (muscles and peripheral motor nerve) system. The cortex, cerebellum, basal ganglia, brainstem and spinal cord are involved in central control of locomotion.

There is increasing evidence for a so-called "central pattern generator" in the human spinal cord. These complexly organized spinal interneurons are capable of generating rhythmic, alternating limb movements that make up the basic pattern of gait but in and of themselves are not enough to control bipedal gait. (Calancie et al., 1994; Dietz et al., 1994).

Brainstem structures play an important role in influencing equilibrium, balance and gait by generating postural responses and influencing equilibrium and balance by modulating inputs from higher cortical areas. The pedunculopontine nucleus appears to be involved with the initiation and termination of locomotion in animal experiments through its connections to the basal ganglia circuit (Nandi et al., 2002). In animal models, two distinct regions have been identified in the brainstem, one involved in controlling posture and the other with gait. It may be reasonable to assume a similar make-up in the human brainstem (Nutt et al., 1993).

The stepping mechanism appears to be primarily controlled at the spinal cord and brainstem levels (Morris et al., 1994a).

The basal ganglia are involved in a variety of activities including preparation, initiation and execution of motor programs, posture and perception and cognitive functions. The basal ganglia influence the ability to initiate and modulate the gait pattern to meet the appropriate demands of a changing environment.

The cerebellum is important in the coordination and execution of movements, including the appropriate scaling of movements. Its role in postural control is unclear but the cerebellum participates in the regulation of relative timing, sequencing and force generation of muscle activity (Nutt et al., 1993).

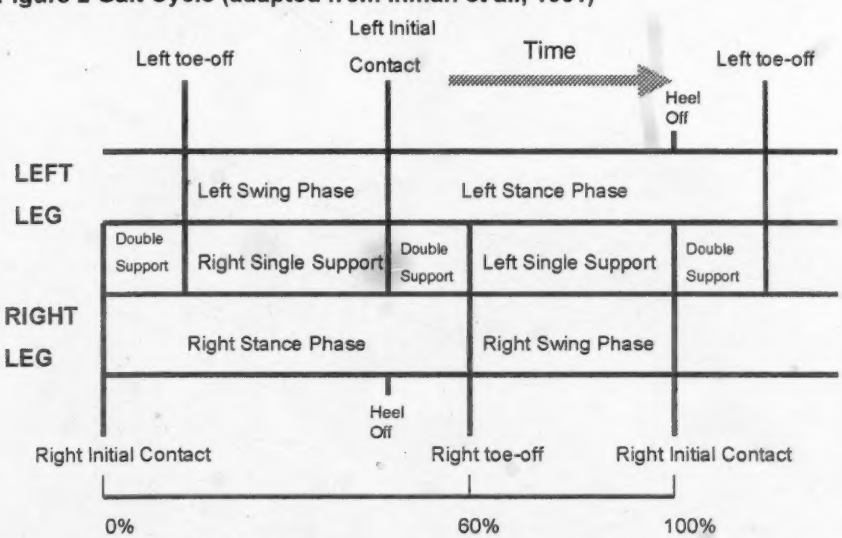
A number of different cortical areas participate in motor control. The primary motor cortex regulates muscle activity through connections to spinal motoneurons. The supplementary motor area (SMA), closely connected with the basal ganglia, is intimately involved in the control of posture and in the preparation of sub-movements and programming of complex motor sequences. Like the SMA, the pre-motor area also has connections to the basal ganglia and is associated with the regulation of whole movement programs (Iansek et. al, 1995).

Locomotion can be considered as a well-learned, highly automatic movement program where the relative timing of muscle activation is fairly fixed and the speed, force production and muscle selection is variable, depending on the requirements of the goal of the individual at a given time (Shapiro et al., 1981). In order for smooth, coordinated motion to occur, all components of the system need to be functioning properly.

The descriptors of gait can be divided into a number of categories. The most often measured and reported are those that relate to spatial and temporal characteristics. These include velocity, step length (the linear distance between successive contacts of opposite feet), cadence (step frequency) and stride length (linear distance between foot to floor contact for the same foot). Kinematics describing changes in joint angles, kinetics describing the forces used to control gait, and electromyography (EMG), describing the electrical activation and activity of muscles, all require relatively sophisticated technology to capture.

The gait cycle is the time interval or sequence of movements that occurs between two consecutive initial contacts for the same foot (see figure 2). It is divided into the swing phase and the stance phase. Each of the phases is then subdivided, identifying individual components of gait. The stance phase occurs when the foot is on the ground bearing weight, can be subdivided into initial contact (heel strike), loading response, single-leg support (mid-stance), heel off (terminal stance) and toe-off (pre-swing). Swing phase which occurs when the foot is non-weight bearing and moving forward, has sub-phases of initial swing (acceleration), mid-swing and terminal swing (deceleration). The double support phase describes that part of the gait cycle when both feet are on the ground.

Figure 2 Gait Cycle (adapted from Inman et al., 1981)



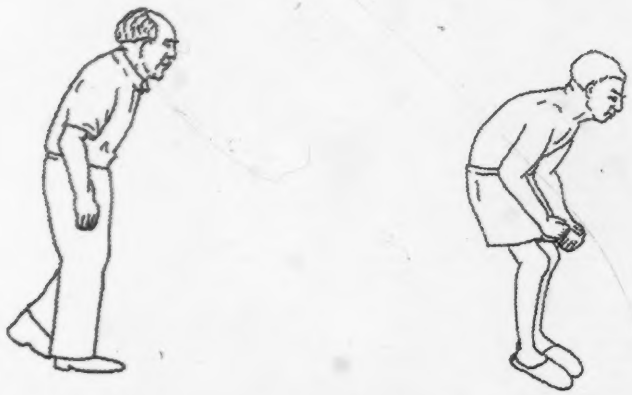
Gait Cycle = 1 Stride (100%)

4 Gait in Parkinson's disease

In Parkinson's disease, disruption of normal locomotion may be minimal initially and become increasingly problematic and disabling as the disease progresses (Hoehn and Yahr, 1967). Medications become less effective and predictable in their action on locomotion (Giladi et al., 1992b; Lamberti et al., 1997; Nieuwboer et al., 1998). The symptoms of bradykinesia, akinesia, rigidity and deficits of postural control all contribute to decreased gait performance. The degree of mobility impairment can fluctuate in response to medication and extremes of gait disturbance can be observed in the same individual depending on whether they are in the "off" or "on" state.

The characteristic picture of advanced parkinsonian gait includes a stooped posture (with pronounced trunk, hip, knee and elbow flexion) perhaps a result of increased rigidity, a kyphotic thoracic spine and consequent "chin poke", reduced or absent arm swing and trunk rotation, a short, shuffling step pattern, bradykinesia and a tendency to turn en bloc. (See figure 3.) The inability to control momentum may lead to uncontrolled movement and falls. Festination describes a progressive increase in walking speed with increasingly shortened steps. The individual appears to be trying to "catch-up" with his or her centre of mass. When this takes place in a forward direction it is termed propulsion and when it takes place in a backward direction it is termed retropulsion. The inability to generate momentum results in disrupted gait with impaired initiation of movement. The corrective mechanisms of anticipatory postural adjustments and a tendency to sway forward add to instability. When these gait difficulties are coupled with impairment of postural control, falling becomes a real threat to safe mobility (Koller et al, 1989). Adding to functional mobility impairment is the appearance of the phenomena of freezing (discussed in Chapter 5), dyskinesia and dystonia.

Figure 3 Posture in later-stage Parkinson's disease



A number of studies have examined the spatio-temporal characteristics of gait in an attempt to elucidate the underlying mechanisms of the disruption of locomotion. Slowing of gait has been observed and appears to be related to reduced stride length, decreased cadence and an increase in time spent in the double support phase (Knutson, 1972). Blin et al. (1990) concluded that there was no significant difference between subjects with Parkinson's disease and normal controls in the relationship between velocity, stride length and cadence at different walking speeds. In contrast, Morris et al. (1994) suggested that for a given walking speed, the stride length in subjects with Parkinson's disease was shorter and the cadence higher than in control subjects and no difference in the time was spent in the double support phase. In testing 34 subjects with Parkinson's disease and 34 age-matched controls where the velocity was fixed, parkinsonian subjects were unable to regulate stride length by internal motor control mechanisms and instead, took shorter steps and increased their cadence. In contrast, they could adjust their cadence when external cues were given to fix the stride length. These authors and others (Krystkowiak et al., 2003) concluded that the underlying cause of slowness of gait in Parkinson's disease was related to the inability to automatically regulate stride length through internal mechanisms.

In another study looking at 54 subjects, Morris et al. (1996a) determined that with appropriate visual cues or attentional strategies, a normal stride length could be generated and that when distracted, the gait pattern degenerated. These studies point to relatively preserved gait control and stepping response (which is primarily controlled at the spinal cord and brainstem levels) with abnormal execution, evidenced by alteration in cadence regulation. They suggest that the basal ganglia dysfunction is responsible for the stride length disruptions seen in Parkinson's disease. The basal ganglia closely interact with SMA in the execution of well-learned motor programs such as locomotion. The dysfunction of the basal ganglia may disrupt motor set for whole movement sequences or disturb the internal cue for sub-movement preparation resulting in an under-scaling of successive steps. Evidence that stride length and velocity are influenced by external cues suggests the interrupted internal cuing mechanism of the basal ganglia and the SMA that normally controls the performance of motor sequences, can be by-passed. Employing cognitive, visual, auditory or motor tricks or cues may allow the individual to abandon the automatic gait mode and switch to a more cortically mediated gait program.

In a recent study examining gait abnormalities in the presence of subthalamic nucleus deep brain stimulation, Krystkowiak et al. (2003) pointed to a role for the subthalamic nucleus in stride length regulation, pointing out that deep brain stimulation of the globus pallidus does not have a significant effect on stride length. In contrast, Defebvre et al. (2002), studied gait following chronic bilateral pallidal stimulation and found improvement in velocity by an increase in stride length. Although there are some clues as to the underlying mechanisms involved in parkinsonian gait, much work remains to fully understand this complex problem.

Stance and swing phases are altered in parkinsonian gait. Among the changes seen in stance phase is that heel-strike during initial contact is altered from the normal heel-toe contact to flat-foot contact. A flat-foot contact provides more

stability and may be an adaptive strategy to compensate for diminished postural control (Kimmeskamp and Hennig, 2001). During swing phase, the angular displacements are reduced throughout the lower limbs and reduced amplitude and speed of the swing may impair the forward movement of the body (Knutson, 1972).

Treatment with antiparkinsonian medications, particularly levodopa (Shan et al., 2001) can alleviate many of the difficulties associated with gait. In gait performance, levodopa is seen to improve (during the "on" state) stride length, walking speed, increase cadence and improve angular displacement of the hips, knees and ankles (Blin et al. 1991). The positive effects remain relatively stable while the medication is effective in improving parkinsonism, in general (Morris, 1996b).

5 Freezing

Patients with Parkinson's disease, by definition, have difficulty with voluntary movement. A specific type of motor abnormality that often results in significant functional disability is that of freezing. Most commonly associated with gait, the freezing phenomenon is a brief (lasting seconds), transient arrest of voluntary movement, occurring on the background of relatively normal movement. During the freezing of gait (FOG) episode, the individual is unable to lift the feet/foot off the ground and often describes the sensation of having their foot/feet momentarily glued to the ground (Fahn, 1995b). These episodes are seen both in the "off" state (when effects of antiparkinsonian medications are absent or ineffective) and in the "on" state (when medications are effectively treating parkinsonian symptoms such as bradykinesia, tremor and rigidity). Abrupt and unpredictable, these episodes often appear when a change in the normal gait pattern or speed is needed or when stressful situations are encountered (Giladi, 2001).

These arrests in voluntary movement are not unique to Parkinson's disease and are seen in a variety of other conditions including primary progressive freezing gait (Achiron et al., 1993), Parkinson's-plus syndromes (where, in addition to parkinsonian symptoms, there are features that are not part of Parkinson's disease) such as progressive supranuclear palsy (Golbe, 1993), and normal pressure hydrocephalus (Sudarsky et al., 1987); following exposure to the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Ballard et al., 1985), in vascular parkinsonism (Thompson and Marsden, 1987; FitzGerald and Jankovic, 1989, Demirkiran et al., 2001), post-encephalitic parkinsonism (Duvoisin, 1965) and in conditions affecting frontal lobe function (Nutt, 1993). Various authors (Giladi et al., 1997; Giladi and Fahn, 1998) have suggested that when significant FOG is seen either as a presenting symptom or early in the disease process, an etiology other than Parkinson's disease such as progressive supranuclear palsy or vascular parkinsonism should be considered.

5.1 Terminology

Charcot first reported the freezing phenomenon in Parkinson's patients in 1877 (cited in Fahn 1995) when he described their difficulty arising from a chair and in initiating gait. Freezing was subsequently described in this group of patients as start-hesitation by Weschler in 1927 (cited in Fahn, 1995) and later during motor activity, as an abrupt, temporary cessation of on-going movement (Schwab and Chafetz, 1954). There is confusion in the literature, and perhaps in the clinical setting as well, over the use of the term "freezing". It has been used to describe a variety of disturbances of voluntary movement and has been used, by some, interchangeably with the term "akinesia". Akinesia has been used to describe a variety of parkinsonian features, including freezing (Schwab et al., 1954), difficulty switching from one motor pattern to another (Lakke, 1981) as well as poverty of movement and slowness of movement (Narabayashi, 1980). Thus, there are the inconsistencies in the literature when using the terms "freezing" and "akinesia". In an attempt to clarify the terminology used to describe this phenomenon, Giladi (1992b) proposed the term "motor block" be used to "characterize all sudden, short-lasting (second) episodes of breaks in motion as well as inhibitions in executing a movement or switching from one movement pattern to another". This term, however, has not been universally adopted, and the terms "freezing", "motor block" and "akinesia" all continue to be used in the literature. The term "freezing of gait" will be used in this paper to describe the phenomenon of transient breaks in voluntary movement related to locomotion.

5.2 Freezing in Parkinson's disease

Although FOG in Parkinson's disease was described before the introduction of levodopa to treat parkinsonian symptoms and was observed to increase shortly after initiating treatment with levodopa (Barbeau, 1972; Ambani and Van Woert, 1973), attempts to tease out the relative contributions of various factors to the appearance of FOG have only recently been undertaken. Clinically, FOG is a common feature of more advanced disease, related to disease duration but

unrelated to age at disease onset (Stern et al., 1980; Giladi, 1992a; Lamberti et al., 1997). It appears to increase in both frequency and severity with disease progression, negatively impacting on mobility and activities of daily living. (Giladi, 2001c)

A retrospective study (Giladi, 1992b) of 900 patients showed that two major risk factors for the development of freezing are long duration of levodopa treatment and advanced disease. Although this was an important study, a retrospective study is limited in its ability to assign the individual contributions of each of these factors to the development of FOG. Giladi et al. (2001b) assessed FOG in a cohort of 800 subjects enrolled in the DATATOP study with one of four treatment groups (placebo, deprenyl, tocopheral or a combination of deprenyl and tocopheral). No subject in this study was initially treated with levodopa. The end point for this part of the study was the appearance of a positive score for FOG on the Unified Parkinson's Disease Rating Scale (UPDRS). After excluding subjects who presented with FOG at baseline (and, coincidentally, longer disease duration and severity), results for the remaining 743 subjects were examined. The authors concluded that the appearance of FOG in Parkinson's patients seemed to be associated with disease duration and an increase in disease severity as reflected in an overall worsening of standard scoring tools, the UPDRS and the Schwab and England Activities of Daily Living Score. In addition, they identified an initial symptom of gait disturbance as a risk factor for the development of FOG and that FOG was strongly related to other gait abnormalities, poor balance and speech difficulties. This study confirmed an independent role for disease duration as a contributing factor in the development of FOG in Parkinson's disease.

While FOG and its relationship to disease duration has been confirmed by a number of studies (Fahn, 1995b; Lamberti et al., 1997; Giladi et al. 2001c), the role of the duration of treatment with levodopa remains controversial. Levodopa has been implicated as a factor in the development of FOG by various authors

(Barbeau, 1972, 1976; Ambani and Van Woert, 1973; Giladi et al. 1992b) but there are data that challenges this connection. Lamberti et al. (1997) studied 100 patients with Parkinson's disease and found that of the 60 patients who reported FOG, the mean duration of exposure to levodopa therapy was not significantly associated with presence of FOG. This has implications for the pathophysiology of freezing discussed below.

5.3 Manifestations of Freezing of Gait in Parkinson's disease

The manifestations of the freezing phenomenon are most commonly seen during gait, although there are reports of freezing occurring during speech, handwriting and teeth brushing (Narabayashi et al., 1976). FOG is a general term that includes a number of distinct aspects of disruption in normal locomotor activity. While these episodes usually last only seconds, in some individuals they may last much longer, particularly in more advanced disease (Lamberti et al., 1997). They are often distressing and debilitating to the person with Parkinson's disease and their unpredictability may influence decisions with respect to social outings and daily activities. When combined with impairment of postural reflexes, FOG may lead to falls and their consequences (Gray and Hildebrand, 2000).

Perhaps the most commonly seen form of FOG in Parkinson's disease is start-hesitation where, as a person tries to initiate walking, there is a delay before the automatic movements of gait begin. Increased effort to initiate forward momentum is often the first strategy employed to over-come start-hesitation but is generally counter-productive (Andrews, 1973). This start-hesitation was seen in approximately 86% of people with Parkinson's disease who reported freezing episodes (Giladi et al, 1992a, Lamberti et al. 1997). Turn-hesitation refers to trouble completing a turn, where, after the initiation of the turn, movement is halted partway through. A common observation is that one foot will move but the other will feel "stuck". A recent paper by Schaafsma et al. (2003) suggests that this may be the most common subtype of FOG and that previous studies underestimated its frequency in protocols containing too few turns.

Target/destination-hesitation refers to freezing that occurs as a person, walking with relatively normal movement, when approaching a chair, for example, will freeze at a distance away. A fourth sub-category of FOG occurs when there is a visible or perceived obstacle. This type of freezing is seen when people encounter escalators, elevators, revolving doors, crowded space, narrow hallways and door jams. FOG is also seen when there is a time limit for task completion such as crossing a street on a green light or answering a ringing telephone. A final common manifestation of FOG occurs in an open, uncluttered walkway with no obvious distractions. Instead of taking a normal step in these situations, there is a brief period of immobility, usually lasting 1-30 seconds, typically followed by a series of short, shuffling steps before a more normal pattern is re-established. In addition to environmental influences on FOG, there also appears to be an emotional or cognitive component as stress levels and heightened anxiety, fear or general arousal affect freezing episodes (Fahn, 1995b).

The frequency and duration of FOG is highly variable making it difficult to quantify. It has also been observed and now documented (Nieuwboer et al., 1998, Giladi, 2001) that the freezing episodes tend not to occur as frequently in a clinic or lab setting when compared to a person's typical environment. The most frequently used rating scale in Parkinson's disease, the UPDRS, has only two questions (14 & 15) in Section II (ADL) that ask about freezing in relation to gait and falls from a historical perspective and one item (question 29) in Section III (motor) where gait is observed and hesitations can be recorded. In an effort to capture a more accurate impression of the severity and frequency of freezing episodes occurring in the home/community environment, Giladi et al. (2000) constructed and validated a Freezing of Gait Questionnaire (FOGQ). Comprised of 6 questions, the FOGQ uses a time scale to reflect the severity of FOG and assesses FOG unrelated to falls. (See Appendix 1.)

5.4 Gait and FOG in Parkinson's disease

Gait impairments, in general, seen in Parkinson's disease have been studied by numerous authors (Knutson, 1972; Blin, 1990; Morris et al, 1994, 1996, 2001; Krystkowiak et al, 2003), as previously discussed. Few studies have looked specifically at the gait of those who experience FOG. Uneo et al. (1993) described an increase in step frequency and incomplete weight shift from one foot to the other in "frozen" gait. Nieuwboer et al. (2001) studied the characteristics of gait at the onset of freezing in 14 subjects with Parkinson's disease who exhibited "off" freezing. In the steps prior to the onset of freezing, they found the stride length decreased with an increased cadence and time spent in the double-support phase. The increase in double support was suggested to be related to postural instability or an indication of a reduced capacity to prepare to step and the increase in cadence, a disruption of the rhythmic control of gait and an impaired ability to control amplitude. They concluded that the cause of freezing was a combination of an increasing inability to generate stride length on a background of dyscontrol of the cadence of walking.

Hausdorff et al. (2003) compared the gait dynamics (average stride time and variability of stride time) of Parkinson's disease subjects with and without freezing, where the stride time variability was a measure of dyscontrol. They found that despite similar average step rate between the two groups, the stride-to-stride variability was markedly increased in the subjects with FOG in both the "off" and "on" states. The conclusion of this study was that Parkinson's disease subjects with FOG have a continuous gait disturbance manifested by a decreased capacity to regulate stride-to-stride variations in gait timing and ability to maintain stable walking rhythm.

5.5 Pathophysiology of FOG

Although freezing has been identified as an important feature affecting function in Parkinson's disease since 1877, its pathophysiology and clinical course remain largely unknown and poorly understood. While it appears to be associated with

both disease duration and, according to some authors, long-term exposure to levodopa, why only some people with Parkinson's disease experience FOG remains unknown (Giladi et al., 2001c; Ambani and Van Woert, 1973; Barbeau, 1972, 1976; Giladi et al., 1992b; Fahn, 1995b).

While the appearance of FOG in more advanced disease suggests an association with more extensive loss of dopaminergic neurons, there is evidence that non-dopaminergic pathways and pathways connecting frontal lobes to the brainstem locomotor centres or the basal ganglia may be involved in freezing (Narabayashi, et al., 1984; Atchison, et al., 1993;Lamberti et al., 1997). Studies examining the cerebrospinal fluid of patients with Parkinson's disease and freezing showed changes to both the noradrenergic and serotonergic systems that are greater than those seen in patients with Parkinson's disease without freezing (Tohgi et al., 1990). There is some evidence that medications affecting the noradrenergic pathways have a positive effect on freezing in parkinsonism (Narabayashi, et al., 1984, 1986; Tohgi, 1993) but these results have been disputed by other studies (Quinn et al., 1984; Fahn, 1995b).

Freezing of gait was described as a clinically negative motor phenomenon by Fahn (1995b) but studies of FOG using electromyography (EMG) have shown that both agonist and antagonist muscles in the lower leg co-contract during freezing episodes (Andrews, 1973; Ueno et al., 1993). FOG cannot be attributed to leg muscle weakness or decreased tone because of its transient nature with otherwise good motor control (Giladi 1992a). The DATATOP study (Giladi et al., 2001b), examining the development of FOG, failed to find a strong association between FOG and an increase in bradykinesia or rigidity. This supported the earlier suggestion by Fahn (1995b) and Lamberti et al. (1997) that the transient nature of freezing was unrelated to bradykinesia that is, to some degree, often present in these patients.

The variable response of FOG to levodopa underscores the complex nature of freezing and defies an easy explanation for its etiology. The appearance of FOG later in the disease may suggest dopaminergic neuronal loss plays a role. This is supported by the observations that "off" period freezing is often alleviated or diminished with an increase in levodopa or dopamine agonists (Linazasoro, 1996 Proewe and Granata, 1997, Camicioli et al., 1998). However, subjects, with more advanced Parkinson's disease, who had undergone putamenal fetal cell transplantation did not experience a decrease in their "off" freezing episodes. This was despite significant reduction in both "off" bradykinesia and rigidity (Freed et al., 1992). One patient with MPTP - induced parkinsonism underwent bilateral fetal mesencephalic grafts. This patient experienced an almost complete resolution of preoperative "off" freezing and marked reduction of "off" period rigidity and bradykinesia (Widner et al., 1992). So, in a picture of relative static damage essentially limited to the nigrostriatal system, an increase in available dopamine had a positive effect on "off" period freezing in this single subject. The effect of dopamine availability in the caudate and putamen may affect FOG, depending on the underlying disease process but it is not clear-cut.

Equally, and perhaps more, perplexing is the basis for "on" period freezing episodes, appearing when an individual is "optimally" treated from a pharmaceutical perspective. This phenomenon was first described by Ambani and Van Woert (1973) and suggested to be a consequence of long-term exposure to levodopa. While "off" period freezing may respond to increased dopaminergic therapy, "on" state freezing is either not affected or exacerbated by increasing levels of dopaminergic medications. Lamberti et al. (1997) failed to find an ameliorating effect on FOG in the "on" state with the use of dopaminergic agents.

Given these differences, it is possible, as suggested by a number of authors (Kompoliti et. al, 2000, Hausdorff et al., 2003, Schaafsma et al., 2003), that the etiology of "off" freezing and "on" freezing is not the same.

It has been proposed that the freezing episodes are a result of an abnormal retrieval or use of motor programs (Goldberg, 1985). It has been documented that Parkinson's patients have a variety of problems with motor control including performing simultaneous tasks (Schwab and Chafetz, 1954, Talland and Schwab, 1964; Brown and Marsden, 1991; Goldenberg, 1990; Camicioli et al., 1998; Bond and Morris, 2000) and initiating movement (Stelmach et al., 1989) that may be more prominent in Parkinson's disease patients with freezing. Freezing is seen in activities (including gait, handwriting and speech) that appear to require an internal rhythm generator to ensure even, continuous motor performance (Shapiro et al., 1981; Narabayashi & Nakamura, 1985). Disruption of this "pacemaker" may result in motor blocks. Ziv et al. (1999) studying patients with early Parkinson's disease doing a manual tapping task, showed abnormalities in the quantity and quality of motor blocks that was correlated to the presence of FOG. They suggested this pointed to a "defect in the physiological time-keeper which governs internally-cued continuous, repetitive movements."

Studies attempting to elucidate the underlying mechanisms of FOG, in its many manifestations, appear to point to multiple factors, rather than a single cause and this has implications on the management of this functionally disabling feature of Parkinson's disease.

5.6 Management of FOG:

There is no clear-cut approach to treatment of FOG. Clearly, if freezing is seen primarily during "off" periods, a sensible approach would be to optimize medical management to diminish the duration and frequency of "off" periods. "On" period freezing is particularly resistant to medical management and may worsen with increased dopaminergic therapy.

Only a few drugs have been reported to have any effect on FOG. In a small group of subjects with early Parkinson's disease, selegiline appeared to have a beneficial effect on the frequency and risk of FOG (Giladi 1996). The effect disappeared when the drug was withdrawn and in a larger, placebo controlled trial, the group receiving selegiline was no different from the placebo group (Parkinson's Study Group, 1996). In a retrospective study, amantadine showed a trend toward decreased frequency of FOG but a more rigorous study is needed to be able to assess the effect of amantadine on FOG (Giladi et al., 2001c). Finally, DL-threo-3,4-dihydroxyphenylserine, a noradrenaline precursor, (Narabayashi, et al., 1984) was shown to be beneficial in the treatment of FOG in one study but the results could not be duplicated (Quinn et al., 1984).

Given that FOG in both the "off" and "on" states is resistant to pharmaceutical intervention, other strategies can be employed to overcome these episodes. Clinically, patients are observed to use sensory input to overcome freezing episodes. These sensory "tricks" use visual, auditory, cognitive and proprioceptive input to "trigger" resumption of normal movement. Unfortunately, responsiveness to FOG to any of these cues is inconsistent, varying in effectiveness for the same kind of freezing episode (i.e. - start-hesitation, target freezing) and whether the freezing occurs in the "off" or "on" state (Kompoliti et al., 2000). Individuals can therefore not depend on only one type of "trick" to overcome FOG. Stern et al. (1980) documented the manoeuvres employed by 47 patients with Parkinson's disease. (See Table 4.) Various modifications in gait strategies included weight shift, changing walking direction and shaking the legs. Visual cues included stepping over an object, real or imagined, and pushing an object in front of them. Auditory stimuli included following a verbal command from someone else, marching, moving to a metronome or music and a sudden loud noise (clap) from someone else. Cognition was identified as a "trick" by paying particular attention to lifting one limb higher than the other.

A number of these sensory cues have been studied in a systematic fashion. Martin (1967) was the first to describe the effectiveness of visual cues to facilitate

locomotion in FOG in post-encephalitic parkinsonism. The author found that the effectiveness of the visual cue was dependent upon specific characteristics. The most effective cues were contrasting coloured lines, at least 18 inches apart, on the floor perpendicular to the feet and at least one inch wide. Other cues, including lines parallel to the direction of movement, very narrow or very wide lines, lines without a contrasting colour to the floor and lines that zigzagged, did not facilitate locomotion. A recent blood flow study showed differential brain activation in the frontal lobes when patients with freezing gait viewed horizontal versus parallel lines on a treadmill, suggesting that horizontal lines may be more effective in activating the frontal cortex and thereby compensating for dysfunctional basal ganglia (Hanakawa et al., 1999).

Table 4 Various "tricks" to overcome FOG (adapted from Stern et al., 1980)

Gait modification by unaccompanied patient
▪ Altering distribution of body weight
▪ Walking sideways
▪ Rocking movements
▪ Stamping feet or shaking legs
▪ Longer steps; walking briskly
▪ Consciously lifting one limb higher
▪ Sliding one foot backwards then throwing it forward
Assisted by another person
▪ Rhythmical pulling or pushing
▪ Passively elevating patient's knee
Verbal or auditory stimuli
▪ Marching to command
▪ Walking or dancing to music or metronome
▪ Another person's verbal commands
▪ Another person suddenly clapping hands
▪ Talking to self
Visual stimuli
▪ Stepping over objects
▪ Watching other people walk
▪ Pushing an object
▪ Imagining lines to step over
Other stimuli
▪ Complex postural movements associated with clicking fingers
▪ Sudden jerky head movements

The use of the modified inverted walking stick (MIS) as a visual cue was found to be helpful in overcoming "off" freezing (Dietz et al., 1990). (The MIS consists of two pieces of wood - the shorter one attaching to the bottom of the longer one at a 90 degree angle which, when placed perpendicular to the foot provides a visual cue to be stepped over.) The MIS is a rather unwieldy device and may pose a safety hazard to some patients. A less cumbersome device in the form of a laser pointer was found to significantly improve FOG in a small study of Parkinson's disease subjects with "on" freezing (Zhang et al., 1999). Held in the hand, subjects were asked to step on the beam of light to overcome FOG and all subjects were reported to have significant improvement in the initiation of gait. In contrast, Kompoliti et al. (2000) looked at a larger group of subjects with Parkinson's disease and "on" freezing to test the responsiveness of FOG to two different kinds of visual cues, comparing walking speed and frequency of freezing episodes with unassisted walking. The two visual cues were a MIS and a cane with a laser beam projecting onto the floor, perpendicular to the cane. This study showed no difference between unassisted walking and visually cued walking, between either of the cued trials or consistency in response to visual cues. (Of interest to note, despite no statistical difference associated with the use of the cane with the laser, a small number of subjects reported subjective improvement and asked to take it home.) The authors of this study urged caution in providing these kinds of devices without supervision because of potential safety issues.

Surgical intervention does not appear to have a beneficial effect on FOG. While the reported effects of pallidotomy, and GPi DBS and STN DBS on gait disorders suggest that gait velocity and stride length are improved (Stolze et al., 2001; Defebvre et al., 2002; Ferrarin et al., 2002; Krystkowiak et al., 2003), this does not appear to extend to FOG (Stolze et al., 2001). These results are disappointing as FOG is relatively resistant to pharmacological interventions.

6 Botulinum Toxin

6.1 Dystonia

Dystonia is a neurologic syndrome characterized by involuntary sustained muscle contractions. It frequently presents with twisting and repetitive movements and abnormal postures that may be sustained. Dystonia, like FOG involves co-activation of agonist and antagonist muscles. Dystonia can be inherited, sporadic or due to secondary causes, including Parkinson's disease. (Jankovic and Brin, 1991). A diurnal dystonia pattern associated with parkinsonian features may respond dramatically to levodopa or anticholinergic treatment (Nygaard et al., 1991). No anatomical lesion has been identified at autopsy in idiopathic dystonia, but there is convincing evidence that dysfunction in the basal ganglia is involved (Jankovic and Brin 1997). A curious and unexplained feature of dystonia is its responsiveness to tactile or proprioceptive stimuli ("sensory trick") such as, with torticollis, a light touch to the side of the face causing more midline posture of the head. The mechanism of action of these tricks is not clear but evidence suggests that afferent pathways are involved via feedback from the periphery (Fahn et al., 1987b; Leis et al., 1992). These tricks have the effect of temporarily reducing or eliminating abnormal postures or movements in dystonia (Fahn et al., 1987b) and are reminiscent of tricks that have also been found to be helpful in overcoming parkinsonian FOG (Stern et al., 1980). Currently, the main therapeutic modality for the treatment of focal dystonia is botulinum toxin injection.

6.2 Botulinum toxin

Botulinum toxin, a protein complex produced by the bacterium *Clostridium botulinum*, has long been known as an extremely potent neurotoxin, responsible for causing botulism (food poisoning) with an associated high fatality rate. As counter-intuitive as it is, the power of this deadly poison has been harnessed to treat debilitating disorders with virtually no side effects. The discovery that botulinum toxin blocks neuromuscular transmission inducing a "temporary" paralysis (Burgen et al., 1949) led to the development of its current therapeutic

applications. Initially used in humans to treat strabismus, it is now widely used to treat a variety of movement disorders and other conditions, including dystonia.

6.3 Mode of Action

Botulinum toxin (BTX) blocks acetylcholine (Ach) release from presynaptic nerve terminals. Its main effect is on the alpha motor neuron system, but it also appears to act on the parasympathetic cholinergic system. This may mediate its effectiveness in treating excessive salivation (Pal et al., 2000), hyperhidrosis (Naumann et al., 1997) and pain (Arezzo, 2002). In the motor neuron system, BTX causes temporary chemodenervation by binding to presynaptic cholinergic nerve terminals, blocking the release of the neurotransmitter Ach at the neuromuscular junction. Ach is required for neuromuscular transmission and its absence results in a reduction or loss of muscle activity. Botulinum toxin has seven known serotypes (A,B,C,D,E,F,G) each with similar effects but different molecular mechanisms in the multiple steps involved in Ach release. This discussion is limited to serotype A, the most widely used therapeutically. The mechanism of Ach release involves a number of distinct steps (Setler, 2002). BTX is produced as a single-chain peptide held together by a disulfide bond that is cleaved into a heavy chain and a light chain. The heavy chain irreversibly binds to the axon terminals of the cholinergic neurons, causing the formation of an endosome that carries the toxin into the nerve terminal. BTX-A then cleaves the synaptosome-associated protein-25 (SNAP-25) that is involved in the SNARE (soluble N-ethyl-maleimide-sensitive factor attachment protein receptor) complex. The SNARE proteins are essential for the fusion of Ach-containing vesicles with the presynaptic neuronal membrane, allowing release of Ach into the neuromuscular junction. The action of BTX-A on SNAP-25 blocks this release, thereby blocking neuromuscular transmission, with a resultant decrease in muscle activity. This effect is temporary. Neurotransmission is re-established initially through collateral sprouting of the affected axon and the growth of additional motor end-plates and eventually through a return of synaptic function of the original nerve terminals (Meunier et al., 2002).

When BTX is injected into a muscle, it acts not only on alpha motor neurons but also affects gamma motor neurons (intrafusal fibres) of the muscle spindle (Rosales et al., 1996). Embedded in skeletal muscle, muscle spindles contain afferent and efferent fibres that play a role in muscle tone, proprioception and reflexes with consequent influences on posture and movement. A decrease in alpha motoneuron activity may then result from this decreased afferent feedback.

In dystonia, a lack of inhibition resulting in unwanted and excessive muscle activity has been identified at the presynaptic phase of spinal reciprocal inhibition and intracortical inhibition in the motor cortex. BTX-A has been shown to normalise inhibition at both these sites (Priori et al., 1995; Gilio et al., 2000). The net impact of this decreased activity may indirectly effect some "reorganization" in the central nervous system and, indeed, there is evidence that BTX may affect circuits in the spinal cord (Priori et al., 1995). After reviewing the literature on the effects of BTX on dystonia, to explain the observed clinical improvement, Giladi (1997) suggested that, in addition to its action at the neuromuscular junction, BTX-A might act as a continuous "sensory trick", through afferent pathways from the muscle spindles or other poorly defined sensory pathways.

6.4 Clinical Indications

Botulinum toxin injections were introduced into human clinical practice in 1981 to treat strabismus (Scott, 1980) and have since gone on to widespread application for a variety of neurologic conditions characterized by excessive muscle activity as well as other conditions including pain, facial lines, excessive sweating and drooling. The movement disorders that benefit from this treatment approach include strabismus, blepharospasm, hemifacial spasm, dystonia, tremors and tics (Jankovic and Brin, 1997). It is the primary treatment for many forms of focal dystonia (Jankovic and Brin 1991), including the foot dystonia seen in Parkinson's disease.

6.5 Clinical Application and Side Effects

Botulinum toxin Type A (BTX-A), and Type B are currently available for clinical use in North America under the names Botox® and Myobloc®, respectively. Doses are roughly dependent on the size of the target muscle or organ. The measured potency of a standard unit is derived from a mouse assay where 1 U of BTX-A corresponds to the calculated median LD_{50} for intra-peritoneal injections in a group of 18-20 g female Swiss-Webster mice (Jankovic and Brin, 1991). (LD_{50} is the dose that kills 50% of the mice tested.) The skill and experience of the person injecting the BTX is an important factor in obtaining a clinically effective outcome, as doses must be tailored to the individual's presentation and appropriate selection of muscles to inject must be made. Electromyography (EMG) guidance of a Teflon coated needle is often a useful tool in localizing target muscles especially those that are particularly deep.

The beneficial clinical effect of BTX varies from weeks to months with patients experiencing latency between injection and clinical effect of several days (Jankovic and Brin, 1997). The peak effect is seen, on average, around 4 - 6 weeks after the injection. A recent report (Hsiung et al., 2002) confirms long-term efficacy of BTX injections for movement disorders sustained over a 10 year period.

Injections of BTX are generally well tolerated and considered to be extremely safe in the appropriately selected patient. Contraindications to treatment are a known hypersensitivity to the toxin, infection at the injection site and pregnancy. Caution is advised in certain conditions with disturbed neuromuscular transmission (Erbguth et al., 1993). Temporary side effects are usually minor and related to local diffusion of the toxin (excessive muscle weakness). High volumes of injected BTX may cause spread to adjacent muscles that are not the intended target. Transient swallowing difficulty has been reported following injections into neck muscles. Systemically, flu-like symptoms may occur. A small number of patients with long-term exposure to BTX-A develop resistance,

where benefit is no longer obtained even at an increased dose (Hsiung et al., 2002).

Foot dystonia is a common feature of more advanced Parkinson's disease and may be treated with BTX-A injections. A case report (Giladi and Honigman, 1997) described a patient with Parkinson's disease and FOG who also had dystonic foot posturing. The dystonia was treated with BTX-A injections and, unexpectedly, the patient reported a dramatic reduction in FOG shortly after the injections. This prompted the investigators to study 10 patients with various types of parkinsonism and FOG as a predominant symptom. In an open-label fashion, they used 150-300 U of BTX-A injected into up to 6-8 sites in the calf muscles bilaterally. Seven subjects received a single session of BTX-A injections, one subject received three sessions and 2 subjects received five sessions of BTX-A injections. Seven of the ten subjects reported significant improvement in FOG, 2 reported no change and 1 was difficult to assess due to medication changes. (A greater number of injection sessions were not related to the reported effects.) The effect lasted an average of 6 weeks (range 4-8 weeks) (Gurevich et al., 2000). The improvement in FOG in parkinsonism may be explained in part by the indirect effect of BTX-A acting as a prolonged "sensory trick".

The functional disability associated with FOG in Parkinson's disease is difficult to treat with conventional approaches. Preliminary data in the literature (Gurevich, 2000; Giladi 2001a) suggested that open-label injections of BTX-A into calf muscles had a positive effect on FOG. A prospective, randomised, double-blind controlled study was needed in order to evaluate the effectiveness of BTX-A on the phenomenon of FOG in Parkinson's disease.

7 Objective

The objective of this study was to evaluate the effect of BTX-A on the phenomenon of FOG in Parkinson's disease through injections of BTX-A into the gastrocnemius/soleus muscles, looking specifically at the frequency and severity of freezing episodes. We hypothesised that BTX-A would have a beneficial effect on FOG in Parkinson's disease.

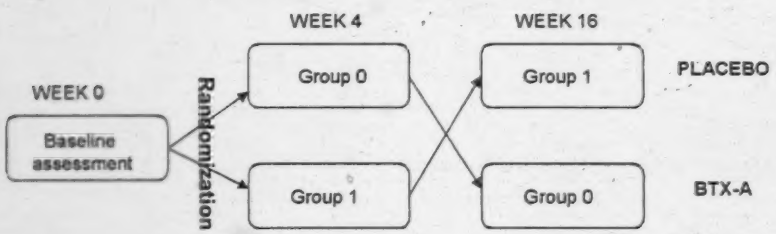
8 Methods

The study took place at the Movement Disorders Clinic located at the Glenrose Rehabilitation Hospital using a University of Alberta Research Ethics Committee approved protocol. Each subject provided informed, written consent.

8.1 Study design

The study employed a two period (AB/BA) crossover design where each subject was randomly allocated to receive either BTX-A followed by placebo injections or placebo followed by BTX-A injections. Subjects, thereby, act as their own "control" (see Figure 4).

Figure 4 Schematic representation of an AB/BA crossover



The biggest threat to the validity of a crossover study design is that of carry-over. If the first treatment given to a subject continues to have an effect into the next period (when the second treatment is given), the baseline may be affected, making the interpretation of any change difficult. A 12 week washout was chosen based on the usual duration of the effects of BTX-A, assuming the subjects will return to baseline. Gurevich et al. (2000) showed an average effect of 7 weeks (range 4-8). In addition we verified that subjects had returned to baseline by doing statistical analysis (see below).

8.2 Methodology

8.2.1 Subject Recruitment

A total of 21 subjects were identified as potential candidates for this study from the Movement Disorders Clinic (MDC) over a period of 2 years. Subjects were

assessed in the MDC to determine study eligibility (see criteria below). Seven subjects declined to participate for a variety of reasons including unreliable transportation to the clinic for the required visits, a sense that the time commitment was too great and a spouse who was not supportive of participation in the trial. One candidate was denied entry into the study after it was deemed that he was unable to understand and complete the diaries required for the study. One subject entered the study but withdrew two weeks after the first injection as he had concurrently developed significant back pain that made any walking difficult. He declined to attend the clinic for a close-out visit, despite several attempts by the investigator to make an appointment, stating that he had to deal with his pain. He was lost to the study.

Inclusion Criteria
▪ a diagnosis of Parkinson's disease with FOG as a major complaint
▪ independent locomotion between freezing episodes
▪ optimally treated with medication for Parkinson's disease, as judged by referring neurologist
▪ stable on medications for at least two months prior to participation in study
Exclusion Criteria
▪ significant cognitive deficits
▪ known hypersensitivity to any ingredient in formulation of BTX-A
▪ inability to keep accurate diaries or attend scheduled visits

8.2.2 Subjects

A total of thirteen subjects with a subjective history of FOG and meeting the inclusion and exclusion criteria consented to participate in the study and were enrolled. Of these, twelve subjects, three women and nine men, age 53 -79 years (mean 67.4 years) and disease duration of 5 -23 years (mean 12 years) completed the protocol. (See Table 5.)

Patients were randomized to receive either BTX-A or saline injection for their first injection at week 4. They received the opposite test medication for their second injection at week 16. Dr. Wayne Martin administered a total of 200 - 300 units of

BTX-A into the gastrocnemius/soleus muscles bilaterally using EMG guidance. Two injections were made into each of the medial and lateral heads of gastrocnemius and two injections into the belly of soleus, for a total of 6 injection sites per leg, 16.25 - 25 units/site and up to 150 units per limb. The dose chosen was based on muscle mass. (The selection of the gastrocnemius/soleus complex for injection was based on previous reports in the literature.)

Table 5 Clinical characteristics of subjects

Subject (Gender)	Age (Years)	Disease Duration (Years)	Hoehn & Yahr	Parkinson's Medications	Early Morning Dystonia
1 (F)	71	7	3	L, CR, Px	no
2 (M)	63	23	2	L, E, P	yes
3 (M)	66	7	2.5	L, CR, P, A	no
4 (M)	75	21	2	L, E, B	yes
5 (F)	57	11	2.5	L, CR, P, A	yes
6 (M)	74	6	3	L, Px	no
7 (M)	60	10	2.5	L, CR, P	yes
8 (F)	79	5	3	L	no
9 (M)	77	15	3	CR, Px	yes
10 (M)	76	9	2.5	L, P	no
11 (M)	58	18	2.5	L, R	yes
12 (M)	53	12	2.5	CR, P, A, T	no

Abbreviations: M = male; F = female; L = levodopa; CR = levodopa controlled release; P = pergolide; Px = pramipexole; R = ropinirole; E = entacapone; A = amantadine; S = selegiline; T = trihexyphenidyl; B= bromocriptine

Marguerite Wieler performed all clinical assessments at the Movement Disorders Clinic. All subjects were assigned a study number and only their initials and study number were used to identify participants. Medical records relating to this study are confidential. All subjects, the clinical evaluator (Marguerite Wieler) and Dr. Martin were blinded to the order of treatment. The blind could be broken if a serious adverse event occurred that required knowledge of the treatment but that was not necessary in this study.

8.2.3 Assessments

Eligible and consenting subjects were seen a total of 6 times over a 28 week period. Clinic visits were 4 weeks apart, ± 2 days. All clinical assessments were completed by the same blinded rater (Marguerite Wieler) at approximately the same time of day to minimise the effect of any diurnal variation on FOG. All subjects were assessed in "on" condition.

Several assessment tools was administered in order to capture the full spectrum of the potential clinical effects of BTX-A (See Appendix 2 for schedule of activities.)

Subjects were required to complete a number of tasks outside of the clinic visits. A Freezing of Gait Questionnaire (Giladi et al. 2000) was used to measure the severity and frequency of FOG. This tool, including 6 questions, assesses FOG severity unrelated to falls. (See Appendix 1.) Diaries recording awake hours and freezing episodes during "off" and "on" periods over three days were used to capture the frequency of FOG. (See Appendix 3.) All subjects were taught how to complete the Freezing of Gait Questionnaire and diaries and practice trials were reviewed to ensure that the subject understood the tool and could reliably complete the questionnaire. The total score of the Freezing of Gait Questionnaire and the frequency of FOG as captured by the diaries were the primary outcome measures.

Data for a number of secondary outcomes were collected. These included subset of items from the UPDRS (Fahn et al., 1987), a widely used valid and reliable tool used to assess the severity of Parkinson's disease motor signs, symptoms and disability. The subset included questions 14 and 15 from Part II of the UPDRS (activities of daily living) relating specifically to freezing and gait, Part III of the UPDRS (motor examination) and Hoehn and Yahr staging (UPDRS Part V). (See Appendix 4.) Timed tests assessed basic mobility in a multiphase task and free walking distance. For the "Timed Up and Go" (Podsiadlo et al.

1991), the subject was seated and asked to rise from an arm chair, stand still momentarily, walk to a line on the floor 3m away, turn, return, turn around and sit down again. The scoring was the time (in seconds) required to complete the task. For the "Two Minute Walk Test" (Light et al., 1997), the subject was asked to walk on a measured 20m walkway at a self-selected, comfortable pace for two minutes for a total of three trials, separated by five-minute rest intervals. The total distance for each trial was recorded and the average distance used in the analysis. A difference in the time required to complete the Timed Up and Go and the distance walked in 2 minutes may be affected by a change in the frequency and/or severity of FOG.

In order to assess the effect of FOG on quality of life, the PDQ-39 (Jenkinson et al., 1995) was administered. The PDQ-39 is a widely used disease-specific tool consisting of 39 items covering eight "domains": mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort. A higher score may reflect a larger impact of Parkinson's disease on quality of life. (See Appendix 5.) A change in the frequency and/or severity of FOG may be reflected in a change in PDQ39 scores.

8.2.4 Statistical analysis

The primary outcome measures were the severity of freezing as reported by the Freezing Questionnaire and the number of freezing episodes as reported on the diaries. Baseline data and week 4 post injection was used in the analyses for primary and secondary outcomes.

Descriptive statistics were expressed as mean, standard deviation and minimum and maximum scores.

To reduce the chances of making Type I errors, a stringent level of significance ($p<0.01$) was set. Independent Student's t-tests were used to examine baseline differences between the groups and assess for carry-over. Paired t-tests were

performed to look for group effects from placebo baseline to four weeks post injection and BTX-A baseline to four weeks post injection without regard to the order of treatment.

All statistical testing was performed with 2-tailed tests. All statistical analyses were performed using the SPSS software version 11.5.0 for Windows.

8.2.4.1 Sample Size considerations

In the absence of quantitative data regarding variability in the measures, no sample size calculations on the primary outcome measures were performed. A previous study reported walking time for a 30 foot course of 14 seconds for subjects with Parkinson's disease with freezing and 10 seconds for subjects with Parkinson's disease without freezing (Camicioli et al, 1998). The standard deviation ranged from 2-6 seconds. Using a parallel group design with 10 subjects per group, a one way analysis of variance with an alpha 0.05, would yield a power of 0.57 to detect a difference of this magnitude between freezing and non-freezing subjects. Assuming that the botulinum toxin treated group had a normal walking speed and the placebo treated group had a walking speed similar to that in the reported study, 12 subjects per group would yield a power of 0.90 to detect a difference of this magnitude. No data were available to calculate sample size for the questionnaires used for the primary outcome measures.

9 Results

Twelve subjects completed the two study treatment periods. Data from the diaries were not available for subject 10. Although this subject correctly completed practise diaries, there were significant omissions as to "off", "on" and "asleep" times and inconsistent indications as to when/if freezing episodes occurred (often remarks were made in the 'comment section' such as "when he can plan ahead where he is going to walk he does not freeze but if he gets up to answer the phone or door he then freezes"). It was not possible to use his diary data. Because of the need to remain blinded to the intervention and responses to the intervention, the poor quality of the diaries was not detected until the end of the study. Subjects 10 and 12 failed to hand in the PDQ39 for week 16. All other data was available to analysis.

No prolonged adverse events were reported by any subjects. One subject reported a transient side effect, describing that his legs felt a bit "like jelly" about a week after the BTX-A injection, lasting a "couple of days".

Stability of the group was established with independent t-tests ($p>.23$), with no difference detected between the pre-intervention week 0 and the baseline assessment of week 4 (baseline for first injection) in any of the outcome measures.

After stability was established, the data for all assessments were examined at four time points. Data were initially presented in temporal order, without regard for treatment order, for weeks 4,8,16 and 20 (where injections were given at week 4 and week 16). Because there was no evidence of carry-over (as described below), the data for the groups were subsequently pooled and labelled placebo baseline, placebo week 4, BTX-A baseline and BTX-A week 4. The data for the primary outcomes measures are reported here.

Descriptive statistics were expressed as mean, standard deviation and range scores. (See tables 6A, 6B, 7A, 7B and figures 5 and 6.)

Table 6 Freezing of Gait Questionnaire (FOGQ) Total Score

A. Absolute time, divided into groups according to order of interventions

	N	Mean	Median	Std. Deviation	Minimum	Maximum
Group 0* week 4	6	17.2	18.0	2.6	13.0	20.0
Group 1* week 4	6	17.0	16.5	2.2	14.0	20.0
Group 0 week 8	6	17.3	18.0	2.8	14.0	20.0
Group 1 week 8	6	16.7	16.0	3.3	12.0	22.0
Group 0 week 16	6	17.0	17.5	3.0	13.0	20.0
Group 1 week 16	6	15.7	15.0	1.9	14.0	18.0
Group 0 week 20	6	17.0	17.0	2.8	14.0	20.0
Group 1 week 20	6	16.3	15.5	2.8	13.0	21.0

* Group 0 = placebo/BTX-A
* Group 1 = BTX-A/placebo

B. Relative time, pooled according to intervention

		N	Mean	Median	Std. Deviation	Minimum	Maximum
Placebo	baseline	12	16.4	16.5	2.3	13.0	20.0
	week 4	12	16.8	16.5	2.7	13.0	21.0
BTX-A	baseline	12	17.0	17.0	2.5	13.0	20.0
	week 4	12	16.8	16.0	2.9	12.0	22.0

Table 7 Diary Data

A. Absolute time, divided into groups according to order of interventions

Total Awake Hours Per Day

	N	Mean	Median	Std. Deviation	Minimum	Maximum
Group 0* week 4	6	15.5	15.1	1.0	14.7	17.3
Group 1* week 4	5	15.0	15.3	1.9	11.8	16.7
Group 0 week 8	6	15.6	15.5	0.5	15.0	16.2
Group 1 week 8	5	15.2	15.8	1.6	12.5	16.2
Group 0 week 16	6	15.5	15.3	0.7	14.5	16.7
Group 1 week 16	5	15.6	16.2	1.1	14.0	16.5
Group 0 week 20	6	15.7	15.6	0.6	14.8	16.7
Group 1 week 20	5	15.5	15.3	1.0	14.2	16.8

* Group 0 = placebo/BTX-A
* Group 1 = BTX-A/placebo

Table 7 - Diary Data continued

A. Absolute time, divided into groups according to order of interventions

FOG Episodes Per Day

	N	Mean	Median	Std. Deviation	Minimum	Maximum
Group 0* week 4	6	6.1	6.8	3.6	1.3	11.2
Group 1* week 4	5	4.9	5.7	2.1	2.2	7.2
Group 0 week 8	6	5.0	4.8	3.2	1.3	9.0
Group 1 week 8	5	6.2	5.7	2.1	4.3	9.8
Group 0 week 16	6	4.5	3.4	4.2	0.5	11.0
Group 1 week 16	5	5.6	3.3	5.2	2.0	14.5
Group 0 week 20	6	4.2	2.0	4.6	0.0	10.8
Group 1 week 20	5	5.5	3.0	6.3	2.2	16.8

* Group 0 = placebo/BTX-A
* Group 1 = BTX-A/placebo

Mean FOG Episodes Per Awake Hour

	N	Mean	Median	Std. Deviation	Minimum	Maximum
Group 0* week 4	6	0.4	0.4	0.2	0.1	0.7
Group 1* week 4	5	0.3	0.4	0.2	0.1	0.6
Group 0 week 8	6	0.3	0.3	0.2	0.1	0.6
Group 1 week 8	5	0.4	0.4	0.1	0.3	0.6
Group 0 week 16	6	0.3	0.2	0.3	0.0	0.7
Group 1 week 16	5	0.4	0.2	0.3	0.1	0.9
Group 0 week 20	6	0.3	0.1	0.3	0.0	0.7
Group 1 week 20	5	0.3	0.2	0.4	0.1	1.0

* Group 0 = placebo/BTX-A
* Group 1 = BTX-A/placebo

B. Relative time, pooled according to intervention

Awake Hours

	N	Mean	Median	Std. Deviation	Minimum	Maximum
Placebo baseline	11	15.5	15.3	1.0	14.0	17.3
Placebo week 4	11	15.5	15.3	0.7	14.2	16.8
BTX-A baseline	11	15.3	15.3	1.3	11.8	16.7
BTX-A week 4	11	15.5	15.7	1.1	12.5	16.7

B. Relative time, pooled according to intervention - continued

Fog Episodes Per Day

	N	Mean	Median	Std. Deviation	Minimum	Maximum
Placebo baseline	11	5.9	6	4.2	1.3	14.5
Placebo week 4	11	5.2	3	4.6	1.3	16.8
BTX-A baseline	11	4.7	5.5	3.3	0.5	11.0
BTX-A week 4	11	5.1	5.2	3.7	0	10.8

Mean Fog Episodes Per Awake Hour

	N	Mean	Median	Std. Deviation	Minimum	Maximum
Placebo baseline	11	0.4	0.4	0.3	0.1	0.9
Placebo week 4	11	0.3	0.2	0.3	0.1	1.0
BTX-A baseline	11	0.3	0.3	0.2	0	0.7
BTX-A week 4	11	0.3	0.3	0.2	0	0.7

Figure 5 Freezing of Gait Questionnaire - grouped according to order of interventions (mean ± SD)

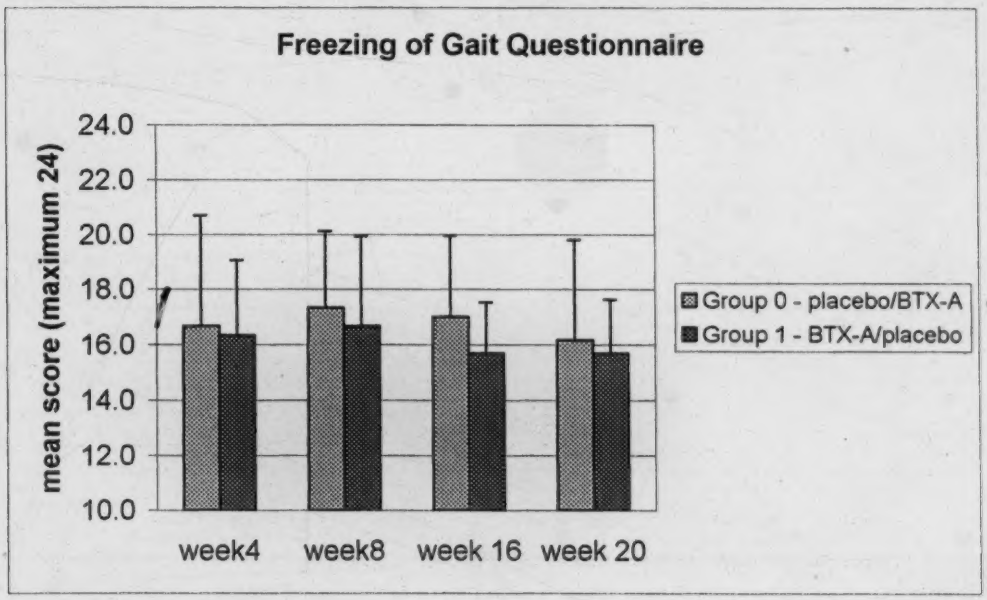
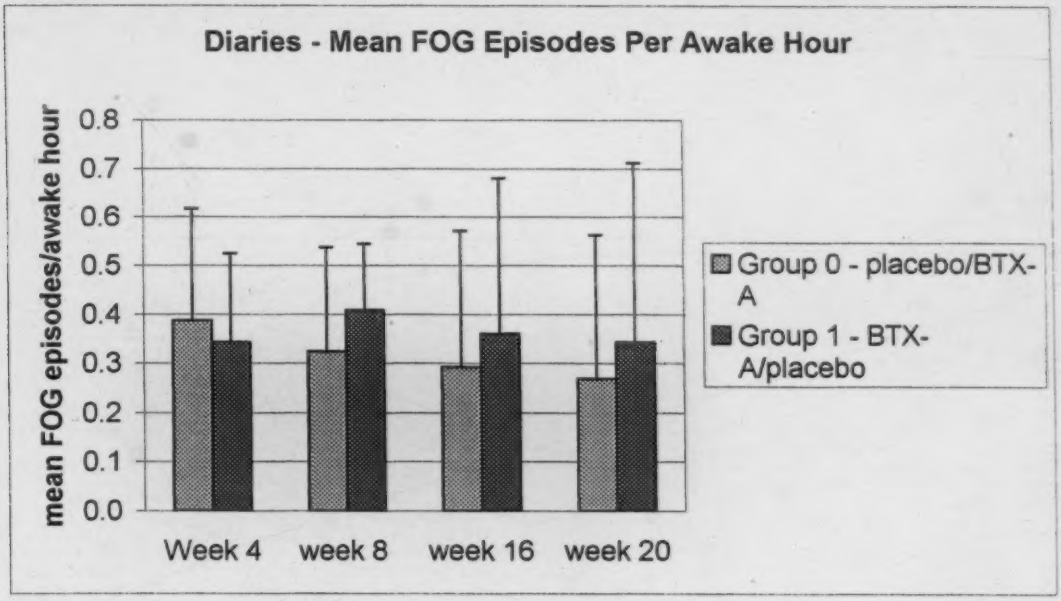


Figure 6 Diary Data - grouped according to order of interventions (mean ± SD)



The data were examined using an independent t-test comparing the 2 groups for week 0 and week 4 to ensure baseline comparability between the groups. Additional independent t-tests were completed to determine that there was no carry-over effect. No significant differences were detected for the FOGQ ($p>.37$) or any of the diary measures ($p>.47$). (See Tables 8 and 9.)

Table 8 Freezing of Gait Questionnaire - Independent t-test for carry-over effect

	t	df	Sig. (2-tailed)	95% Confidence Interval of the Difference	
				Lower	Upper
Week 4	0.17	10	0.870	-4.10	4.76
Week 8	0.38	10	0.712	-3.25	4.58
Week 16	0.93	10	0.373	-1.85	4.52
Week 20	0.30	10	0.774	-3.28	4.28

Table 9 Diary Data - Independent t-test for carry-over effect

		t	df	Sig. (2-Tailed)	95% Confidence Interval Of The Difference	
					Lower	Upper
Week 4	Total awake hours	0.49	9	0.64	-1.59	2.47
	FOG Episodes per day	0.62	9	0.55	-3.01	5.28
	Mean FOG episodes per awake hour	0.35	9	0.73	-0.24	0.33
week 8	Total awake hours	0.49	9	0.64	-1.17	1.82
	FOG Episodes per day	-0.73	9	0.48	-5.03	2.58
	Mean FOG episodes per awake hour	-0.76	9	0.47	-0.34	0.17
week 16	Total awake hours	-0.21	9	0.84	-1.33	1.11
	FOG Episodes per day	-0.41	9	0.69	-7.56	5.24
	Mean FOG episodes per awake hour	-0.38	9	0.71	-0.48	0.34
week 20	Total awake hours	0.39	9	0.70	-0.93	1.32
	FOG Episodes per day	-0.41	9	0.69	-8.78	6.10
	Mean FOG episodes per awake hour	-0.37	9	0.72	-0.53	0.38

The differences were calculated between a) the baseline placebo and week 4 of the placebo and b) baseline intervention and week 4 of the intervention. These differences were then compared using an independent t-test. No significant differences were detected for the FOGQ ($p>.18$) or any of the diary measures($p>.71$). (See Table 10.)

Table 10 Differences between baseline, week 4 (placebo and BTX-A) - Independent t-test

	N	Mean	Std. Deviation	t	df	Sig. (2-Tailed)	95% Confidence Interval of the Difference	
							Lower	Upper
FOGQ	12	-0.92	2.19	-1.45	11	0.18	-2.31	0.48
Total awake hours	11	-0.06	1.07	-0.17	10	0.87	-0.77	0.66
FOG episodes per day	11	-0.19	2.35	-0.26	10	0.80	-1.77	1.39
Mean FOG episodes per	11	-0.02	0.14	-0.38	10	0.71	-0.11	0.08

To look for difference over time relative to the intervention and placebo, paired t-tests were performed. No significant differences were seen for any measure for the FOGQ (p>.32) or any of the diary measures (p>.23). (See Table 11 and 12.)

Table 11 Freezing of Gait Questionnaire - Paired t-test comparing differences over time relative to placebo and BTX-A

	Mean	Std. Deviation	t	df	Sig. (2-Tailed)	95% Confidence Interval of the Difference	
						Lower	Upper
Placebo baseline-placebo week 4	-0.42	1.38	-1.05	11	0.32	-1.29	0.46
BTX-A baseline- BTX-A week 4	0.17	1.80	0.32	11	0.75	-0.98	1.31

Table 12 Diary Data - Paired t-test comparing differences over time relative to placebo and BTX-A

		Mean	Std. Deviation	t	df	Sig. (2-Tailed)	95% Confidence Interval of the Difference	
							Lower	Upper
Placebo baseline-placebo week 4	Total awake hours	-0.01	0.73	-0.04	10	0.97	-0.50	0.48
	FOG Episodes per day	0.63	1.91	1.10	10	0.30	-0.65	1.92
	Mean FOG episodes per awake hour	0.04	0.11	1.27	10	0.23	-0.03	0.12
BTX-A baseline-BTX-A week 4	Total awake hours	-0.21	0.66	-1.07	10	0.31	-0.66	0.23
	FOG Episodes per day	-0.43	2.58	-0.55	10	0.59	-2.17	1.30
	Mean FOG episodes per awake hour	-0.02	0.16	-0.35	10	0.73	-0.13	0.09

Similar analyses were performed for the secondary outcome measures: 2 Minute Walk, Timed Up and Go, PDQ39 and UPDRS questions 14 and 15. No significant differences were seen with any of these measures. (See Appendix 6.)

When asked to give an overall impression of how and if their FOG had changed following any of the interventions, nine of twelve subjects reported no change in the severity or frequency of their FOG. Subjective comments by 3 subjects (Subjects 4, 9 and 12) suggested improvement from the BTX treatment that was not captured by any of the assessment tools. Subjects 4 and 12 reported a decrease in the frequency of FOG episodes that were not reflected in the FOGQ or diaries. Subject 12 requested to continue with the BTX injections. Subject 10 reported a significant decrease in night time leg cramps after the BTX injection, lasting approximately 3 weeks.

The net result of the analyses was that there was no significant difference seen between placebo and BTX-A on any of the primary variables or on the secondary variables.

10 Discussion

The principle motivation of this work was to evaluate a potential treatment for FOG in Parkinson's disease. This is a disabling feature of advanced disease that responds poorly to existing medical and surgical interventions. The main result of our study was that BTX-A did not improve the signs or symptoms related to FOG.

The objective of the current study was to examine, in a double-blind fashion, the effect of up to 150 U of BTX-A versus placebo (saline) injections, bilaterally, into the calf muscles in subjects with FOG and a diagnosis of idiopathic Parkinson's disease. This study examined the frequency and severity of FOG, timed tests relating to gait performance, quality of life and UPDRS scores relating to gait. The intervention was shown to be safe and well tolerated. Unfortunately, no difference was detected in FOG with any of the clinical assessments following either intervention.

Candidates selected were those with a diagnosis of Parkinson's disease with FOG as a major complaint, good locomotion between freezing episodes, and an optimal and stable medication regime. The presence of dystonia was not an inclusion criterion. The initial report of the beneficial effect of BTX-A on FOG was observed in the presence of foot dystonia (Giladi, 1997) and, indeed, Giladi et al. (2001a) reported the best response of open label BTX-A injections was seen in 4 of 6 subjects with concomitant foot dystonia. In the current study, despite the presence of early morning dystonia in half of the subjects, no response to BTX-A was detected in any subject, suggesting that early morning dystonia is not associated with any response of FOG to BTX-A injections. This was not examined statistically as this was not a planned analysis and since there was no trend detected for an effect of BTX-A, no further analysis was performed.

Previously published data on open-label BTX-A injections and FOG in parkinsonism (Giladi, 2001a) showed a benefit in FOG in 70% of subjects. This was a heterogeneous group of 10 subjects, however, with parkinsonism from various etiologies. The authors urged caution when interpreting the results and acknowledged that it would be important to conduct a more rigorous study examining FOG in Parkinson's disease.

The great variability in the frequency, nature and severity of FOG makes it difficult to have a control group that closely resembles the treatment group. Thus, an examination of FOG lends itself to a crossover design. A crossover trial design has several advantages. It is very efficient because each subject acts as his/her own control, reducing the number of subjects needed to form adequate conclusions. It compares treatments within each patient and the influence of patient characteristics is "subtracted" out. It also removes an important source of variability (between patient variability), important in conditions with great variability in the factor of interest between subjects (Senn, 1993).

The study, as conducted, had a number of limitations. The frequency, severity and duration of FOG are highly variable between and within individuals and are difficult to quantify. The tools available to characterize FOG remain inadequate. This is emphasised by the subjective report of improvement with BTX-A injections by 25% of subjects that was not reflected in any of the measurements used in this study.

Subject education was a critical aspect in appropriately choosing candidates for study participation. It was crucial that subjects be able to differentiate freezing episodes from "off" periods as motor fluctuations may be mistakenly identified as freezing episodes. The concept of the transient nature of freezing episodes on a background of relatively good ambulation needed to be reinforced with the subjects. As discussed in the previous section, despite this precaution, one subject who did well with the practise diaries (with education also provided to the

spouse) failed to complete the diaries appropriately once the interventions started.

The use of diaries to capture the frequency of freezing episodes has other inherent problems. While diaries capture the total awake hours, hours "off" and "on" and occurrence of freezing within a half hour block, the diaries did not capture times when subjects were sitting or did not attempt to move and may have underestimated the impact of freezing on quality of life. A number of subjects reported that they sat for long periods watching TV, reading or doing crafts and could not report, had they tried to move during those times, if they would have experienced FOG. It would be ideal to capture the exact number of freezing episodes rather than just the appearance of freezing within a half hour period. The logistics and current tools available to document this, however, make it unworkable.

The Freezing of Gait Questionnaire, comprised of 6 items (each on a 5 point scale where 0 reflected an absence of the symptom and 4 indicated the most severe stage) may have had a ceiling effect where subtle or slight improvements may not have been captured.

The documentation of FOG using diaries and the Freezing of Gait Questionnaire required that subjects be compliant in filling out the forms at the appropriate time. Specific written instructions were given to each subject as to the timing of each form but it is possible that subjects did not strictly adhere to the timelines, which would introduce a source of error to the data.

Although several gait measures were performed in the research setting, none of these were affected by BTX-A. Various authors (Nieuwboer, 1998, Giladi, 2001a) have observed that FOG episodes are seen less frequently in a clinic setting than reported in the individual's normal environment. Indeed, many of the spouses of the subjects in the current study observed a significant improvement

in the subject's walking ability during the study visits at the clinic, expressing the wish that that walking ability would transfer to the home environment. Environmental influences on FOG may be relevant and difficult to control for in a lab or clinic setting. This reflects the inherent challenge in capturing the nature, severity, frequency and triggers of FOG in Parkinson's disease.

Subject recruitment was more difficult than originally anticipated. Over a 2 year period, only 21 suitable candidates were identified. This may be an underestimation of total suitable candidates as identification rested on the efforts of busy clinic staff whose primary responsibilities were to address the clinical needs of the patients seen in the clinic. Reinforcement of recruitment efforts was made periodically in an effort to ensure as complete identification of suitable candidates as possible. Several potential subjects or their spouses perceived the requirements of the study as too onerous further decreasing the number of subjects available for the study. Analysis of the diaries showed all but one subject had both "off" and "on" FOG. This may further limit our ability to generalize to patients with pure "off" or "on" FOG. While these limitations may affect the generalizability of the results, the subjects were chosen as typical of patients with FOG seen the Movement Disorders Clinic.

Other problems relate to the use of a single injector and single evaluator but practical concerns necessitated this design. The advantage is that inter-rater and inter-injector reliability were not a factor. The injections were EMG guided into an active area of muscle but muscle spindles were not specifically targeted, a factor that may be important in affecting afferent feedback.

The mechanism of freezing, including FOG in Parkinson's disease, remains unknown. Some studies have implicated dysfunction in noradrenergic and serotonergic systems (Narabayashi et al., 1984; Tohgi et al., 1993; Sandyk, 1996). A similar pathophysiology for dystonia and freezing has also been suggested (Fahn, 1995b). FOG shares some features with focal dystonia, a

syndrome where injections of BTX often provide symptomatic relief. BTX is known to block neuromuscular transmission resulting in transient muscle weakness. There is also evidence of an indirect effect on the central nervous system (Priori, 1995; Gilio, 2000). Preliminary data in the literature suggests injections of BTX-A into calf muscles had a positive effect on FOG with a suggested mode of action through afferent pathways from muscle spindles to act as a long lasting and effective "sensory trick" (Giladi, 1997). Our data do not support this notion, suggesting that afferent muscle spindle input may not be critical determinants of FOG.

11 Future Considerations

Limitations of the current study have been identified. A future study of FOG in Parkinson's disease and BTX-A injections might be improved with the inclusion of more subjects as the current study included a small number. In the absence of data on FOG, a sample size was estimated from gait ranges in a previous study on FOG and gait in Parkinson's disease. Data from this study can be used in the design of a future study. Given that there was no significant difference detected with BTX-A, it is unlikely that, given the same study conditions, this would change with a larger sample size.

The known effect of BTX-A on dystonia may make the presence of foot dystonia (beyond "early morning dystonia") in the context of FOG an important inclusion criterion for use of BTX-A. With the inclusion of a broader group of subjects, a planned sub-group analysis for this group would be appropriate.

The current study restricted the dose to a minimum of 100 U and a maximum of 150 U per leg, based on previous reports in the literature and the known safety of BTX-A. However, this may have been inadequate, resulting in the absence of an effect of BTX-A on FOG. The optimal dose is not known but is a question that could be addressed in a future dose-response study. The selection of the gastrocnemius/soleus complex for injection was also based on previous reports where it was suggested that the weakening of the calf muscles would interfere with normal gait activation and force a switch to a more conscious gait pattern. In a future study it might be worth exploring other muscle groups of the lower leg such as extensor hallucis longus, tibialis posterior or tibialis anterior, which may be involved in the co-contraction seen in FOG.

The lack of sophisticated objective gait analysis in the current study may have missed subtle effect of BTX-A on FOG. A more rigorous examination of various gait parameters would add to the understanding of FOG in general and, more

specifically, any effect of BTX-A. It would be important to devise a route where the likelihood of provoking FOG would be maximized such as including walking through a narrow passage or doorway.

Freezing has been associated with an increased incidence of falling in people with Parkinson's disease (Gray and Hildebrand, 2000), and any future study looking at FOG in Parkinson's disease may be more inclusive if a record of falls and circumstances surrounding falls was reported but this would likely require a larger sample size.

A suggested mechanism of the effect of BTX-A on dystonia (Giladi, 1997) involved the afferent fibres of the muscle spindles. In this study, the dose of BTX-A was reasonable from a clinical perspective and should have resulted in a change in the afferent input from the muscle spindles. Although this was not measured, it may be that the effect of afferent muscle spindle activity is not relevant in FOG seen in Parkinson's disease. A better understanding of the basis of FOG in Parkinson's disease would allow for exploration of other treatment options for this debilitating problem.

It was intriguing that one of the reported subjective benefits from the BTX-A injection was not related to freezing. This subject reported a decrease in night time leg cramping. It may be interesting to further explore the treatment of night time leg cramping with BTX-A in individuals with concomitant FOG.

The lack of evidence for any effect of BTX-A on FOG in this group of subjects with idiopathic Parkinson's disease, while disappointing, should not remove it from potentially playing a role in the treatment of FOG. A dose-response study with a larger sample size, incorporating foot dystonia as an inclusion criterion, would answer the crucial questions raised by this study. This study underscores the need to continue to explore alternative options to address debilitating phenomenon, FOG in Parkinson's disease.

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13 Appendices

13.1 Appendix 1 - Freezing of Gait Questionnaire (FOGQ)

FREEZING OF GAIT QUESTIONNAIRE

1. During your worst state – Do you walk: ☐

   0 Normally
   1 Almost normally – somewhat slow
   2 Slow but fully independent
   3 Need assistance or walking aid
   4 Unable to walk

2. Are your gait difficulties affecting your daily activities and independence? ☐

   0 Not at all
   1 Mildly
   2 Moderately
   3 Severely
   4 Unable to walk

3. Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)? ☐

   0 Never
   1 Very rarely - about once a month
   2 Rarely - about once a week
   3 Often – about once a day
   4 Always – whenever walking

4. How long is your longest freezing episode? ☐

   0 Never happens
   1 1-2 seconds
   2 3-10 seconds
   3 11-30 seconds
   4 Unable to walk for more than 30 seconds

5. How long is your typical start hesitation episode? ☐

0 None
1 Takes longer than one second to start walking
2 Takes longer than 3 seconds to start walking
3 Takes longer than 10 seconds to start walking
4 Takes longer than 30 seconds to start walking

6. How long is your typical turning hesitation? (Freezing when turning) ☐

0 None
1 Resume turning in 1-2 seconds
2 Resume turning in 3-10 seconds
3 Resume turning in 11-30 seconds
4 Unable to resume turning for more than 30 seconds

13.2 Appendix 2 - Schedule of Activities

SCHEDULE OF ACTIVITIES

A Double-blind Placebo Controlled Cross-over Pilot Study of Botulinum Toxin (Botox®) to Treat Freezing of Gait in Parkinson's Disease

VISIT	1	2		4	5		7	8
WEEK	0	4	6	8	16	18	20	28
CLINIC VISIT	X	X		X	X		X	X
PDQ39*	X			X	X		X	X
Diary	X	X	X	X	X	X	X	X
Freezing Questionnaire	X	X	X	X	X	X	X	X

*PDQ39 – Parkinson's Disease Questionnaire 39

DIARY

Name _____ Date _____

Please mark the appropriate response below for each 30 minute assessment by **shading** the area. Also note the timing of medication using the medication abbreviations. (see below).

	6 am	7 am	8 am	9 am	10 am	11 am	12 noon	1 pm	2 pm	3 pm	4 pm	5 pm	6 pm	7 pm	8 pm	9 pm	10 pm	11 pm
MEDS																		
OFF																		
ON																		
Freezing episodes																		
ASLEEP																		

Comments: _____

_____

Medications:
S = Sinemet **SCR** = Sinemet Controlled Release
P = Prolopa **Px** = Permax **M** = Mirapex **R** = Requip

Example:

	7 am	8 am
MEDS		
OFF		
ON		
Freezing episodes		

13.4 Appendix 4 - Subset of Unified Parkinson's Disease Rating Scale (UPDRS)

II. ACTIVITIES OF DAILY LIVING

14. Freezing when walking

0 = None.
1 = Rare freezing when walking; may have start hesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking

0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

III. MOTOR EXAMINATION

18. Speech

0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression

0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)

0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands

0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity

0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

Subset of Unified Parkinson's Disease Rating Scale (UPDRS) - continued

29. Gait

0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability

0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia

0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

V. MODIFIED HOEHN AND YAHR STAGING

STAGE 0 = No signs of disease.
STAGE 1 = Unilateral disease.
STAGE 2 = Bilateral disease, without impairment of balance.
STAGE 2.5 = Mild bilateral disease, with recovery on pull test.
STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.
STAGE 4 = Severe disability; still able to walk or stand unassisted.
STAGE 5 = Wheelchair bound or bedridden unless aided.

13.5 Appendix 5 - Parkinson's Disease Questionnaire 39 (PDQ39)

DUE TO HAVING PARKINSON'S DISEASE, how often have you experienced the following, during the last month?

Due to having Parkinson's disease, how often during the last month have you	*Please tick one box for each question*				
	Never	Occasionally	Sometimes	Often	Always or cannot do at all
1. Had difficulty doing the leisure activities which you would like to do?	☐	☐	☐	☐	☐
2. Had difficulty looking after your home, e.g. DIY, housework, cooking?	☐	☐	☐	☐	☐
3. Had difficulty carrying bags of shopping?	☐	☐	☐	☐	☐
4. Had problems walking half a mile?	☐	☐	☐	☐	☐
5. Had problems walking 100 yards?	☐	☐	☐	☐	☐
6. Had problems getting around the house as easily as you would like?	☐	☐	☐	☐	☐
7. Had difficulty getting around in public?	☐	☐	☐	☐	☐
8. Needed someone else to accompany you when you went out?	☐	☐	☐	☐	☐
9. Felt frightened or worried about falling over in public?	☐	☐	☐	☐	☐

Please check that you have ticked one box for each question before going on to the next page

Due to having Parkinson's disease, how often <u>during the last month</u> have you....	*Please tick one box for each question*				
	Never	Occasionally	Sometimes	Often	Always
10. Been confined to the house more than you would like?	☐	☐	☐	☐	☐
11. Had difficulty washing yourself?	☐	☐	☐	☐	☐
12. Had difficulty dressing yourself?	☐	☐	☐	☐	☐
13. Had problems doing up buttons or shoe laces?	☐	☐	☐	☐	☐
14. Had problems writing clearly?	☐	☐	☐	☐	☐
15. Had difficulty cutting up your food?	☐	☐	☐	☐	☐
16. Had difficulty holding a drink without spilling it?	☐	☐	☐	☐	☐
17. Felt depressed?	☐	☐	☐	☐	☐
18. Felt isolated and lonely?	☐	☐	☐	☐	☐

Please check that you have ticked one box for each question before going on to the next page.

Due to having Parkinson's disease, how often <u>during the last month</u> have you	*Please tick one box for each question*				
	Never	Occasionally	Sometimes	Often	Always
19. Felt weepy or tearful?	☐	☐	☐	☐	☐
20. Felt angry or bitter?	☐	☐	☐	☐	☐
21. Felt anxious?	☐	☐	☐	☐	☐
22. Felt worried about your future?	☐	☐	☐	☐	☐
23. Felt you had to conceal your Parkinson's from people?	☐	☐	☐	☐	☐
24. Avoided situations which involve eating or drinking in public?	☐	☐	☐	☐	☐
25. Felt embarrassed in public due to having Parkinson's disease?	☐	☐	☐	☐	☐
26. Felt worried by other people's reaction to you?	☐	☐	☐	☐	☐
27. Had problems with your close personal relationships?	☐	☐	☐	☐	☐

Please check that you have ticked one box for each question before going on to the next page

Due to having Parkinson's disease, how often <u>during the last month</u> have you	*Please tick one box for each question*				
	Never	Occasionally	Sometimes	Often	Always
28. **Lacked support in the ways you need from your spouse or partner?** *If you do not have a spouse or partner tick here* ☐	☐	☐	☐	☐	☐
29. **Lacked support in the ways you need from your family or close friends?**	☐	☐	☐	☐	☐
30. **Unexpectedly fallen asleep during the day?**	☐	☐	☐	☐	☐
31. **Had problems with your concentration, e.g. when reading or watching TV?**	☐	☐	☐	☐	☐
32. **Felt your memory was bad?**	☐	☐	☐	☐	☐
33. **Had distressing dreams or hallucinations?**	☐	☐	☐	☐	☐
34. **Had difficulty with your speech?**	☐	☐	☐	☐	☐
35. **Felt unable to communicate with people properly?**	☐	☐	☐	☐	☐
36. **Felt ignored by people?**	☐	☐	☐	☐	☐

Please check that you have ticked one box for each question before going on to the next page

Due to having Parkinson's disease, how often <u>during the last month</u> have you	*Please tick one box for each question*				
	Never	Occasionally	Sometimes	Often	Always
37. Had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
38. Had aches and pains in your joints or body?	☐	☐	☐	☐	☐
39. Felt unpleasantly hot or cold?	☐	☐	☐	☐	☐

Please check that you have ticked one box for each question

Thank you for completing the questionnaire

13.6 Appendix 6 - Secondary Outcome Measures

Table 13 Secondary Outcome Measures - Descriptive Statistics

	N = 12	Mean	Median	Std. Deviation	Minimum	Maximum
2 Minute Walk (metres)						
Placebo	baseline	115.9	131.0	43. 7	13.0	154.0
	week 4	121.1	136.5	44.5	29.0	163.0
BTX-A	baseline	117.2	137.5	52.7	8.0	169.0
	week 4	113.4	132.5	44.6	23.0	165.0
Timed Up and Go (seconds)						
Placebo	baseline	39.2	11.5	79.9	7.9	287.0
	week 4	23.7	12.4	30.7	7.7	115.0
BTX-A	baseline	26.3	11.3	36.6	8.4	135.0
	week 4	24.3	11.9	39.4	7.0	148.0
PDQ39						
Placebo	baseline mobility	52.9	60.0	18.6	10.0	75.0
	baseline ADL*	26.9	26.4	14.1	5.6	50.0
	baseline SI*	27.9	28.8	9.5	11.5	38.0
	week4 mobility	59.2	60.0	21.4	22.5	100.0
	week4 ADL	28.7	22.2	16.3	8.3	66.7
	week4 SI	31.5	29.3	14.5	13.1	57.5
BTX-A	baseline mobility	51.7	51.3	27.2	12.5	92.5
	baseline ADL	25.7	20.8	14.5	5.6	47.2
	baseline SI	28.7	28.5	10.5	16.2	44.1
	week4 mobility	57.5	57.5	18.6	25.0	80.0
	week4 ADL	25.3	22.2	16.9	5.6	55.6
	week4 SI	29.4	28.1	14.1	14.6	60.0

*ADL - Activities of Daily Living, *SI - Summary Index

Figure 7 2 Minute Walk - Mean Walking Distance grouped according to order of interventions (mean ± SD)

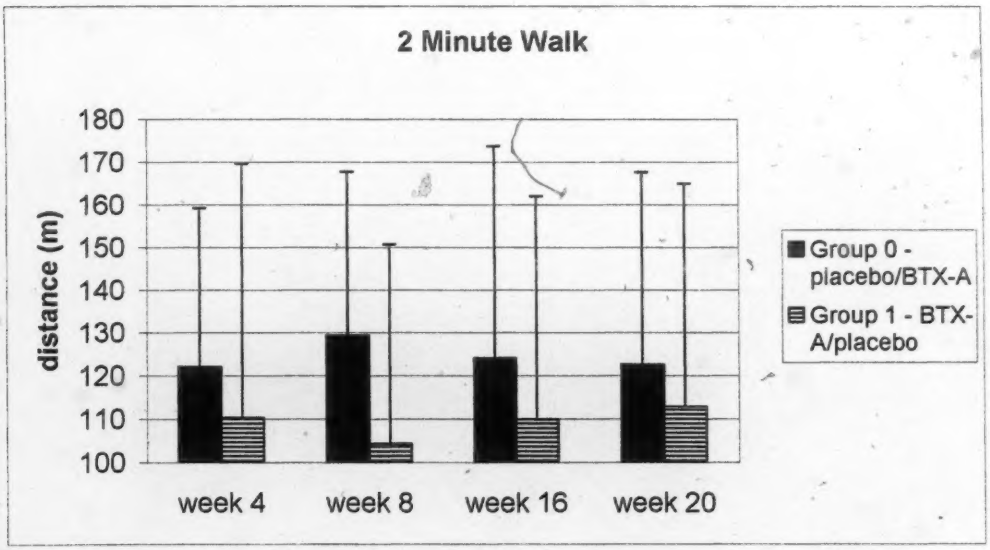

Figure 8 Timed Up and Go grouped according to order of interventions (mean ± SD)

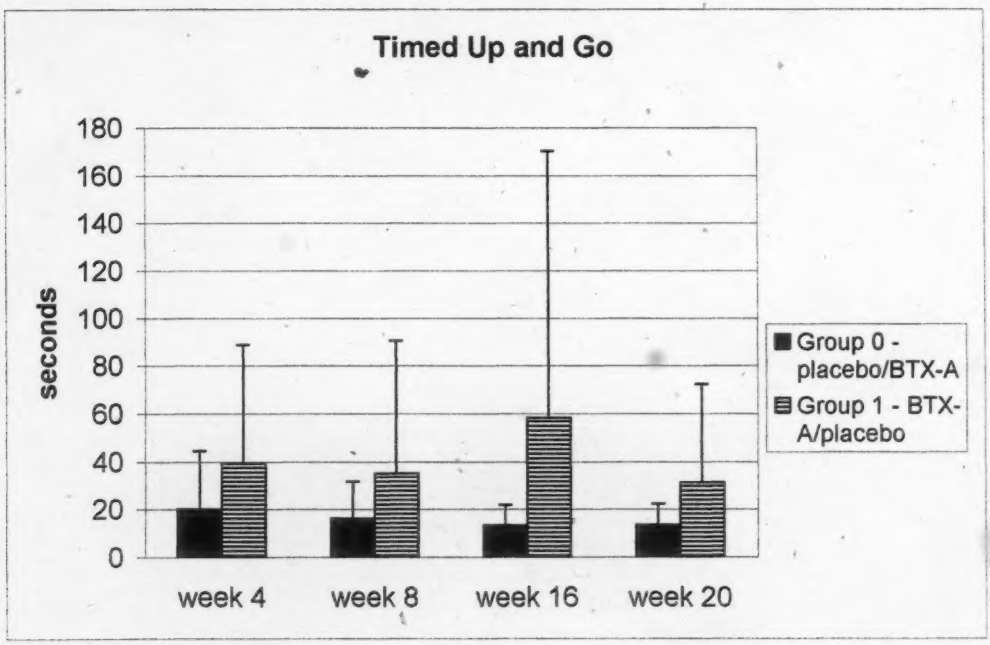

Table 14 Secondary Outcome Measures - Independent t-test - Differences between placebo baseline, placebo week 4 and BTX-A baseline, BTX-A week 4

	N	Mean	Std. Deviation	t	df	Sig. (2-Tailed)	95% Confidence Interval of the Difference	
							Lower	Upper
2Minute Walk (metres)	12	0.3	20.0	0.04	11	0.97	-12.46	12.96
Timed Up and Go (seconds)	12	13.5	55.8	0.84	11	0.42	-21.97	48.97
PDQ39 mobility	10	-2.5	22.5	-0.35	9	0.73	-18.56	13.56
PDQ30 ADL*	10	-0.3	14.1	-0.06	9	0.95	-10.34	9.79
PDQ30 SI*	10	2.4	10.4	0.73	9	0.48	-5.06	9.87

*ADL - Activities of Daily Living, *SI - Summary Index

Table 15 Secondary Outcome Measures - Paired t-test comparing differences over time, relative to placebo and BTX-A

		Mean	Std. Deviation	t	df	Sig. (2-Tailed)	95% Confidence Interval of the Difference	
							Lower	Upper
2 Minute Walk (metres)								
placebo baseline-placebo week 4		-5.2	14.1	-1.27	11	0.23	-14.10	3.76
BTX-A baseline- BTX-A week 4		3.8	11.9	1.09	11	0.30	-3.82	11.32
Timed Up and Go (seconds)								
placebo baseline-placebo week 4		4.0	13.8	1.02	11	0.33	-4.72	12.80
BTX-A baseline- BTX-A week 4		13.4	50.0	0.93	11	0.37	-18.40	45.12
PDQ39								
placebo baseline-placebo week 4	mobility	-6.3	10.0	-2.17	11	0.05	-12.59	0.09
	ADL*	-1.9	10.6	-0.60	11	0.56	-8.60	4.89
	SI*	-3.6	8.9	-1.42	11	0.18	-9.27	2.01
BTX-A baseline-BTX-A week 4	mobility	-8	16.5	-1.54	9	0.16	-19.77	3.77
	ADL	-0.6	14.7	-0.12	9	0.91	-11.06	9.95
	SI	-1.0	10.7	-0.29	9	0.78	-8.61	6.67

*ADL - Activities of Daily Living, *SI - Summary Index